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INSTRUMENTATION IN THE CHEMICAL AND PETROLEUM INDUSTRIES

Volume 2

Proceedings of the Chemical and Petroleum Instrumentation sessions held during the First Joint International Symposium on Analysis Instrumentation and Chemical and Petroleum Instrumentation, held May 26-28, 1965, in Montreal, with selected papers from the 20th Annual ISA Conference, held October 4-7, 1965 in Los Angeles

Edited by C. W. Sanders
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Wilmington, Delaware

Papers describe the most recent developments in the application of sophisticated instrumentation to the chemical and petroleum industries. The contributors are experts in their field and describe practical experiments and developmental research.

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THE XXII CONGRESS OF THE COMMUNIST PARTY OF THE SOVIET UNION

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Our country is going through an unprecedented upsurge in work and in political life in connection with the publication of the New Program of the Communist Party of the Soviet Union. Marxist-Leninist principles which reveal the historic meaning of events and the bold plans of the party which are leading to the shining heights of communism naturally cannot fail to stir anyone who believes in the triumph of reason and justice.

The New Program of the CPSU contains a profound scientific analysis of the development of society in the present epoch, and theoretical and practical principles have been worked out in it which will show our people the way toward the building of communism. With exceptional single-mindedness the New Program of the CPSU has defined the problems of governmental, economic and cultural construction the solution of which are essential to the building of a communist society in the USSR.

In the course of building a communist society we must first solve three very important problems: create a material and technical base for communism; transform socialist methods of production into communist ones; educate every Soviet citizen in the spirit of communism, and completely root out the survivals of capitalism from people's minds.

For the solution of these problems an exceptionally large role is assigned to science. Communism and science are inseparable. In determining the outlook for Soviet science the Communisty Party of the Soviet Union is striving to make certain that "with us science – as Lenin said in 1923 – shall not remain a dead letter of a fashionable phrase . . . , but shall actually enter our flesh and blood and become a complete and integral part of our way of life."* Year by year since that time Soviet science has been drawn more closely into the orbit of governmental activity and has penetrated into all the plans for the development of the national economy of the USSR. Day by day and year by year the role of science in our country has been growing ever larger and larger. The New Plan of the CPSU points out that "The Party will in every way possible promote the further strengthening of the role of science in the building of a communist society," and it especially emphasizes the fact that "The use of science will become a decisive factor in the mighty growth of the productive forces of society. The development of science and the introduction of its achievements into the national economy will continue to be a subject of special concern to the Party."

Soviet scholars have the task of taking a leading position in world science and in directing their efforts toward the solution of theoretical problems which will open up broad opportunities for progress in industry, agriculture, medicine, etc. The scope of scientific research and its connection with practical activity must attain a level, as mentioned in the Program, such that "science will become in full measure a direct productive force."

In directing the development of Soviet science and technology, the Communist Party of the Soviet Union and the Soviet government always concentrate attention on the most important and decisive trends.

The construction of a material and technical base for communism demands the solution of problems which will assure a degree of technical progress that the world has never before seen. The New Program of the CPSU, citing a strictly scientific definition of communism, contains an indication of the very important role of science and technology as a base for the growth of the productive forces of the country. "Communism ensures the uninterrupted development of social production and a high productivity of labor on the basis of rapid scientific-technical progress, equips man with the most perfect and mighty technology, raises the mastery of people over nature to a tremendous height and gives everyone the possibility of controlling her elemental forces more fully and completely.

As a matter of fact, in discovering the laws of development of nature and of society, science permits man to control the forces of nature and puts into his hands a mighty tool for controlling and managing them. This is science's

* V. I. Lenin. Soch., t. 33, str. 447.

greatest mission – its chief importance. "As long as we do not know the laws of science – wrote Lenin – it, existing and acting beyond our knowledge, will make us slaves of 'blind necessity'. But once we discover these laws, which act independently of our will and our consciousness (as Marx kept repeating a thousand times), we become the masters of nature."*

The party considers knowledge of the laws of nature, and their utilization in the interests of building communism, to be a task of paramount importance for Soviet science. That is why such great significance is attached to research on decisive trends and problems.

By formulating the tasks of the Party in the field of economic construction, of building and developing a material and economic base for communism, the New Program of the CPSU points out the basic directions of scientific and technical progress.

The material and technical base for communism means – the complete electrification of the country and the perfection of equipment, technology and organization of social production in industry and agriculture on this base; complex mechanization of the processes of production and ever more complete automation; a broad application of chemistry in the national economy; the constant development of new and economically effective branches of production, of new types of energy and materials; thorough utilization of natural resources and an organic union of science with production; a high cultural-technical level of the workers; a significant superiority over the most highly developed capitalist countries in the productivity of labor – these are the most important conditions for the victory of the communist system.

On this base will occur a gradual transformation of socialist methods of production into communist ones which will serve as a foundation for profound improvements in the political organization of society and of its governmental structure and lead to an upsurge in the material and cultural level of the people in terms of the communist education of all members of society.

Building communism on a vast scale will bring forth new and more complicated problems which will have to be completely solved by science in due time.

As the New Program of the CPSU states, the pivot for the construction of a communist society is the electrification of all branches of the national economy. Therefore the question of energy is at the center of attention of Soviet science. The tempo of technological progress is primarily determined by the growth of the energy producing equipment of the country. In assigning to the problem of electrification the chief role in creating a material and technical base for communism, amid all the technological progress of the present day, the Party is following the well-known Leninist formula: "Communism is Soviet state power plus the electrification of the entire country."

Between 1961 and 1980, according to the New Program of the CPSU, the complete electrification of our country will be accomplished. This will mean the reconstruction of the entire national economy on a new technical base corresponding to that of present day heavy industry.

Achievement of the plan of complete electrification proposes the wide application of new sources of energy – the energy of the atom, the sun and the tides – in addition to the well-known types of fuel and hydroelectric resources.

The method now used for the production of electric energy is extremely complex and irrational: chemical energy contained in fuel is first converted into heat energy which is then converted into mechanical energy and finally into electrical energy. The present day level of science is opening up the possibility of finding methods of much more rapid conversion of heat energy into electrical energy without the use of mechanical equipment – by means of thermoelectric and plasma generators which will make it possible to save a great deal of fuel. In order to build such generators it will be necessary to solve a number of complex problems in solid state physics and in plasma physics.

Energy producing equipment is the most important but it is not the only aspect of the material and technical level of production. The other aspect is a system of machines and the technology of production – the implements of work. This subject is given very great attention in the New Program of the CPSU. It presumes the accomplishment of the complex mechanization and automation of production on a massive scale. In the first place this refers to machine construction. A technical revolution in this branch is an indispensable condition for the automation of all other branches of production. The automation of production is the principal condition for lightening labor and increasing its productivity.

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* V. I. Lenin, Soch., t. 14, izd. 4, str. 177.

In the course of accomplishing the twenty year program of development of the national economy of the USSR (1961-1980), complex mechanization a..d automation will be introduced on a massive scale in a great transition to automated shops and factories. A broad application of cybernetics, electronics, and computers is envisaged in production, in engineering design, in calculating plans, in accounting, statistics and in management.

A no less important side of the production process is the problem of materials. The present level of development of technology with its unprecedentedly high speeds, temperatures and pressures requires the creation of new synthetic materials which do not exist in nature. Many types of fuel and raw material will gradually be displaced by new ones which are more productive, with specially designed properties and with previously determined technical characteristics. The use of these materials will open up tremendous opportunities for the further development of science and technology, for the subjugation of nature, for the improvement of life, etc.

The most characteristic materials of the future are the new synthetic products made by organic synthesis – the so-called polymers – plastics, synthetic rubber, leather, fur. These materials will become ever more dominant in industry, in construction and in life. To a considerable degree they can take the place of metals since they have greater durability, resistance to oxidation, etc. The discovery of methods of preparing inorganic polymers with useful properties will have especially important consequences. Raw material sources for them are inexhaustible. Theoretical studies of the molecular structure of matter and of the course of chemical reactions will continually open up new possibilities of preparing synthetic materials, new alloys, etc.

In connection with the above it is essential that research in the field of polymerization and the regulated synthesis of compounds of high molecular weight be greatly broadened. A study of macrostructure and the establishment of a theoretical foundation for making polymers into manufactured articles also becomes extremely important. Chemists will have a great deal of work in researching new types of high-molecular compounds and organo-metallic and inorganic polymers.

Also very important is the solution by chemists of such problems as the preparation of physiologically-active medicinal products, materials for combating plant pests and diseases, herbicides, growth substances, etc. In this field chemistry comes into very close touch with biology. Their "symbiosis" will open up great possibilities for the chemical industry and for agriculture.

The principal attention of Soviet chemists is now focussed on research in the chemistry of high-molecular compounds and on the creation of a mighty synthetic materials industry based on them.

As the sphere of practical utilization of polymers has broadened it has become evident that it is necessary to seek such methods of synthesis as will permit the preparation of materials with properties which are essential for the national economy. In this connection methods of polymerization which are new in principle have been found: "graft polymerization," "block polymerization," the synthesis of strictly ordered (stereoregular) polymers.

The great outlook for the synthesis of polymers with a given set of properties represents a new field of science – mechanochemistry, at the basis of which lies the principle of transforming mechanical energy into chemical energy. Mechanochemistry permits the modification of the properties of polymers and makes possible the study of the behavior of synthetic materials under different conditions. Simultaneously, so-called "chemical mechanics" is springing up; it is the transformation of chemical energy into mechanical energy. The development of this new field of science may lead to the construction of machines whose principle of action is based on the direction conversion of chemical energy to mechanical energy. It will find application in many branches of technology.

Of great importance in the development of the chemistry of high molecular weight compounds is the creation of polymers with semi-conducting and magnetic properties, and the production of fibers with semi-conducting properties which can transmit impulses similarly to the nerves of the living organism.

Great also will be the role of other branches of the natural, engineering and a number of the social sciences in creating a material and technical base for communism. Especially crucial and complex are the problems before the social sciences in working out the transition from socialist production methods to communist ones, and the education of all the citizens of our country in the spirit of communism.

The grandiose proposals contemplated in the New Program of the CPSU lay a great responsibility on Soviet scholars in every branch of science. The program of the Party, whose New Plan is now open for discussion by all the people, will open up broad opportunities for the application of the creative ability of scholars and for their participation in the building of a communist society.

The New Program of the Communist Party of the Soviet Union, like a mighty searchlight, illuminates the multitudinous problems, trends and prospects of scientific and cultural progress in connection with the building of a communist society. The Party's slogan, proclaimed in the New Program of the CPSU "Everything in the name of man, for the good of man" will inspire Soviet men of science to great new achievements.

THE DIELECTRIC PERMEABILITY OF TWO-LIQUID SYSTEMS CONSISTING OF POLAR COMPONENTS

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The applicability of measurements of dielectric permeability of liquid systems for determining interactions between components has been established by a number of studies [1-7]. The majority of the studies were devoted to an examination of benzene solutions of these systems. The use of physical chemical methods of studying liquid systems in solution, along with some positive advantages, does have some substantial disadvantages [8]. Because of this, a study of the polar properties of liquid systems must be carried out both in solution and without solvents. This makes it possible to show a number of new regularities and to investigate the behavior of systems consisting of components with very similar or strongly differing dipole moments.

We have studied the dielectric permeability of a number of two-liquid systems. In the case of some systems the dielectric permeability was measured at various temperatures.

The dielectric permeability was determined by the pulse method which we described previously [9]. The components of the systems studied were subjected to careful purification by the usual methods. The purified substances and the solvents were kept in sealed ampoules. Concentration is always expressed in molar portions. During the measurements every precaution was taken against the penetration of moisture.

All the systems studied by us may be divided into three groups. In the first group are systems whose components have dipole moments that are closely similar (Table 1) and whose isotherms of dielectric permeability are linear. In the second group are systems formed from components whose dipole moments differ from one another (Table 2). For these systems the deviations of the experimental values of dielectric permeability from additivity have a negative sign. In the third group are systems with positive deviations of dielectric permeability from the additive value (Table 3). In the latter case the equality and difference of the values of the dipole moments do not, apparently, play a significant role. The results of studies of the dielectric permeability of systems belonging to the first group are shown in Figs. 1-5.

As can be seen from the data presented, the isotherms of dielectric permeability for all eight systems are straight lines throughout the entire concentration interval.

A change in the temperature does not interfere with the linear character of the isotherms of dielectric permeability, and the maximum deviation of the latter from additivity (Table 1) does not exceed 0.9% at any temperature.

The isotherms of two-liquid systems whose components are normal non-dipole liquids are linear throughout the concentration interval. Similar systems behave normally [10, 11]. On comparing the isotherms of dielectric permeability of the systems we studied with the permeability isotherms of systems formed from normal non-dipole components (Table 1) one may conclude that systems composed of polar components that do not react chemically and which have closely similar dipole moments, should be close to normal in their behavior. This is confirmed by the results of studies of other physical chemical properties of analogous systems [12-14].

The behavior of these systems may apparently be explained in the following way. If the first approach toward association is viewed as an orientation of the molecules of the polar liquid in the internal field, the relation between the number of disoriented (dissociated) molecules and the total number of molecules may be expressed by the following equation [15]:

$$N = N\left[1 - L^2\left(\frac{\mu E}{kT}\right)\right], \qquad (1)$$

TABLE 1. Systems of the First Group

System	Dipole moment of 1st component (in D)	Dipole moment of 2nd component (in D)	Maximum deviation from additivity (in %)
Acetone – methylethylketone	2.76	2.79	0.5
n-Propyl alcohol – n-butyl alcohol	1.66	1.66	0.4
Dimethylaniline – diethylaniline	1.59	1.65	0.4
Isoamyl acetate – methyl ester of caproic acid	1.82	1.76*	0.2
Methylethylketone – benzaldehyde	2.79	2.75	0.1
Diethylaniline – methyl ester of caproic acid	1.65	1.76*	0.3
Pyridine – quinoline	2.25	2.18	0.9
Dimethylaniline – chlorobenzene	1.59	1.55	0.5

* The dipole moment of the methyl ester of caproic acid was determined by us in benzene at 25°.

TABLE 2. Systems of the Second Group

System	Dipole moment of 1st component (in D)	Dipole moment of 2nd component (in D)	Maximum deviation from additivity (in %)
Isobutyl alcohol – nitrobenzene	1.79	3.96	–13.2
Isobutyl alcohol – acetone	1.79	2.76	–15.9
Isobutyl alcohol – cyclohexanone	1.79	3.01	–24.3
Isobutyl alcohol – aniline	1.79	1.48	–23.0
n-Propyl alcohol – diethyl ether	1.66	1.10	–30.0
Methyl acetate – piperidine	1.75	1.17	– 3.3

TABLE 3. Systems of the Third Group

System	Dipole moment of 1st component (in D)	Dipole moment of 2nd component (in D)	Maximum deviation from additivity (in %)
Quinoline – chloroform	2.18	1.10	+23.6
Quinoline – aniline	2.18	1.48	+13.6
Pyridine – aniline	2.25	1.48	+10.6
Chloroform – diethyl ether	1.10	1.22	+33.2
Chloroform – methyl acetate	1.10	1.75	+18.8
Chloroform – dibutyl ether	1.10	1.18	+17.0
Aniline – diethyl ether	1.48	1.22	+14.4
Chloroform – benzyl acetate	1.10	1.80	+11.3
Titanium tetrachloride – ethyl ester of trichloroacetic acid	0	2.55	+36.3

where N' is the number of disoriented molecules, $L^2\left(\frac{\mu E}{kT}\right)$ is the Langevin function, μ is the dipole moment, E is the internal field, k is the Boltzmann constant, T is the absolute temperature.

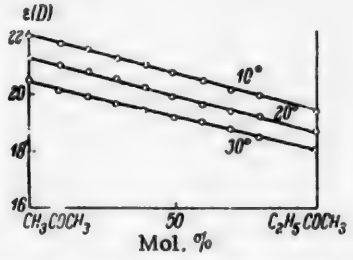

Fig. 1. Dielectric permeability of mixtures: $CH_3COCH_3 - C_2H_5COCH_3$.

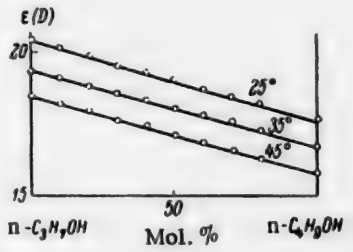

Fig. 2. Dielectric permeability of mixtures: $n\text{-}C_3H_7OH - n\text{-}C_4H_9OH$.

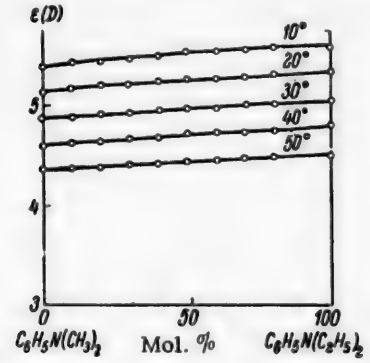

Fig. 3. Dielectric permeability of mixtures: $C_6H_5N(CH_3)_2 - C_6H_5N(C_2H_5)_2$.

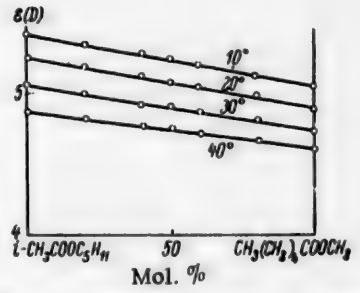

Fig. 4. Dielectric permeability of mixtures: $iso\text{-}CH_3COOC_5H_{11} - CH_3(CH_2)_4COOCH_3$.

From equation (1) it is evident that the degree of disorientation of the molecules of a polar liquid in the internal field is dependent on the magnitude of the dipole. On mixing two polar liquids with closely similar values of the internal fields and dipole moments, the degree of disorientation of the molecules of each of the components remains, within a first approximation, the same as that of the pure liquid. Of course this only occurs when the components do not react chemically with one another. As a matter of fact, in the case of the reaction of two similar polar molecules with a dipole moment μ, the potential energy of orientation will be equal to [16]

$$U_0 = -\frac{2}{3} \cdot \frac{\mu^4}{kTr^6}, \qquad (2)$$

where r is the distance between interacting dipoles.

If, however, two unlike molecules with dipole moments μ_1 and μ_2 interact with each other, the potential energy of orientation U'_0 in this case will be equal to

$$U'_0 = -\frac{2}{3} \cdot \frac{\mu_1^2 \cdot \mu_2^2}{kTr^6}. \qquad (3)$$

From the latter equation it is apparent that when the dipole moments are equal ($\mu_1 = \mu_2$), the potential energies of orientation of similar and unlike molecules become identical; consequently the molecular state of the components should not change on mixing. It is true that in equations (2) and (3) the induction effect was not taken into consideration; however taking it into consideration does not result in any substantial changes since the interacting molecules have identical dipole moments.

The results of studies of the dielectric permeability of systems belonging to the second group are shown in Figs. 6-8. In the last column of Table 2 are shown the relative deviations of the experimental values of the dielectric

permeability from additivity. From the data given it is clearly evident that the isotherms of dielectric permeability of all the systems studied, with the exception of the system methyl acetate-piperidine, have significant negative deviations from the additive value. This fact may be explained by the elimination of the chain association of the alcohol molecules at the expense of the hydrogen bond.

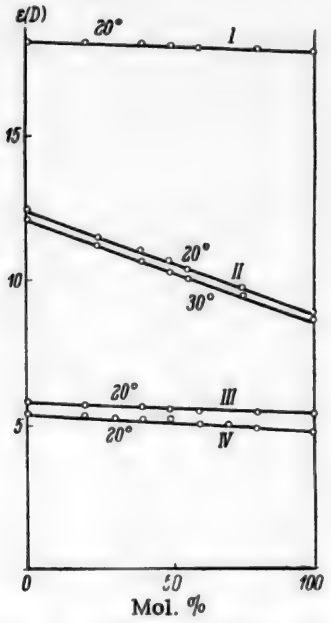

Fig. 5. Dielectric permeability of mixtures: I) $C_2H_5COCH_3 - C_6H_5CHO$; II) $C_5H_5N - C_9H_7N$; III) $C_6H_5Cl - C_6H_5N(CH_3)_2$; IV) $C_6H_5N(C_2H_5)_2 - CH_3(CH_2)_4 \cdot COOCH_3$.

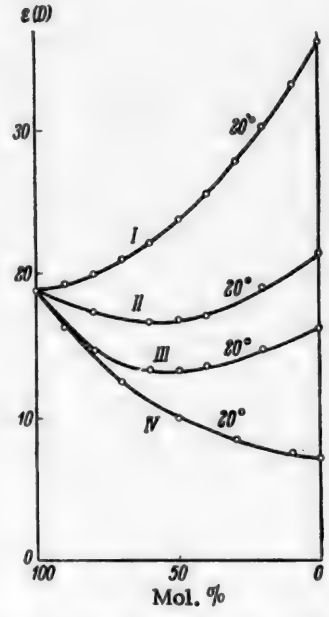

Fig. 6. Dielectric permeability of mixtures: I) iso-$C_4H_9OH - C_6H_5NO_2$; II) iso-$C_4H_9OH - CH_3COCH_3$; III) iso-$C_4H_9OH - C_6H_{10}O$; IV) iso-C_4H_9OH – $- C_6H_5NH_2$.

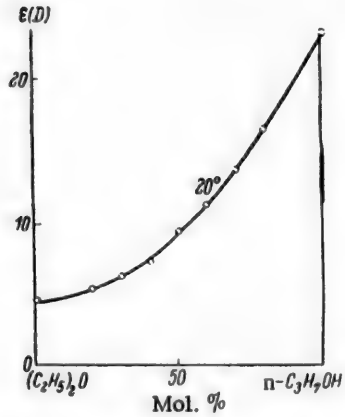

Fig. 7. Dielectric permeability of mixtures: $(C_2H_5)_2O - n\text{-}C_3H_7OH$.

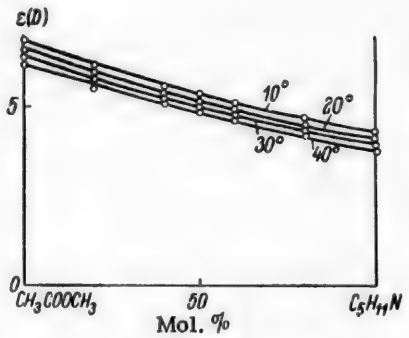

Fig. 8. Dielectric permeability of mixtures: $CH_3COOCH_3 - C_5H_{11}N$.

In analyzing the experimental data of Table 2, attention should be drawn to the following interesting fact. There is no definite connection between the relative deviations of the dielectric permeability of systems from additivity and the difference between the dipole moments. This phenomenon may apparently be explained as follows. In the first place, the ability of a given molecule dipole to interact with dipoles of adjacent molecules depends to a considerable degree on the location of the given dipole [17]. The data of Table 2 show that the difference between

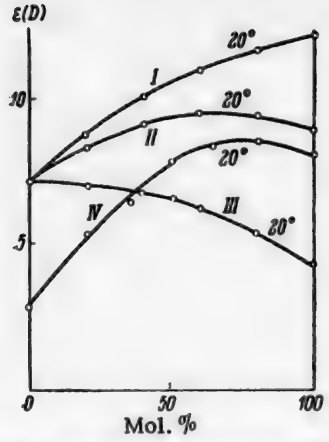

Fig. 9. Dielectric permeability of mixtures: I) $C_6H_5NH_2 - C_5H_5N$; II) $C_6H_5NH_2 - C_9H_7N$; III) $C_6H_5NH_2 - (C_2H_5)_2O$; IV) $TiCl_4 - CCl_3COOC_2H_5$.

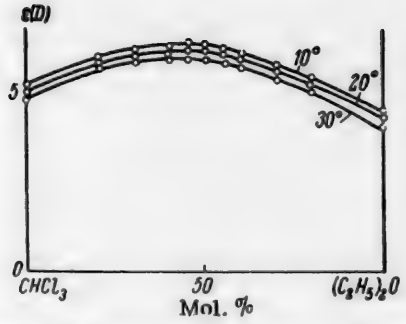

Fig. 10. Dielectric permeability of mixtures: $CHCl_3 - (C_2H_5)_2O$.

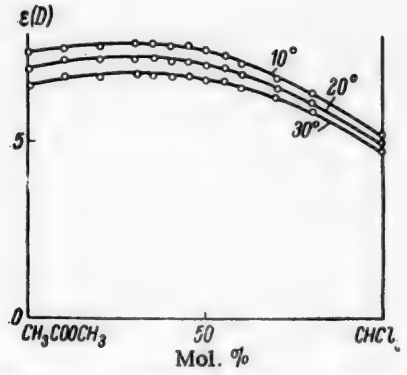

Fig. 11. Dielectric permeability of mixtures: $CH_3COOCH_3 - CHCl_3$.

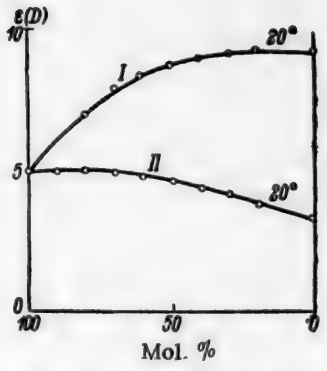

Fig. 12. Dielectric permeability of mixtures: I) $CHCl_3 - C_9H_7N$; II) $CHCl_3 - (C_4H_9)_2O$.

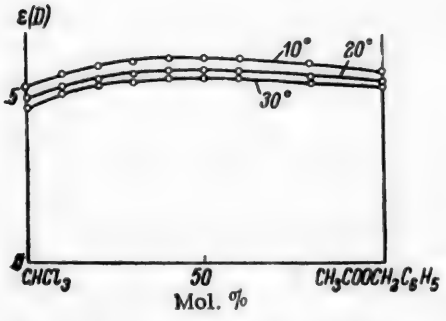

Fig. 13. Dielectric permeability of mixtures: $CH_3COOCH_2C_6H_5 - CHCl_3$.

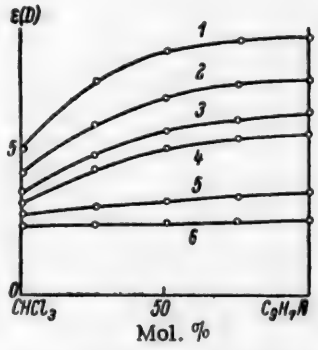

Fig. 14. Dielectric permeability of mixtures in benzene: content of benzene in mol. %: 1) 0.0; 2) 20.0; 3) 40.0; 4) 50.0; 5) 60.0; 6) 80.0.

the dipole moments of nitrobenzene and isobutyl alcohol is considerably greater than the difference between the moments of the same alcohol and acetone, aniline and cyclohexanone. However the relative deviation of the dielectric permeability from additivity in the isobutyl alcohol – nitrobenzene system is considerably less than in the other systems. The fact is that the dipole of nitrobenzene is located far from the surface of the molecule, and since the strength of the field created by this dipole decreases proportionally to distance by the third power, the influence of the nitrobenzene dipole on the association of alcohol is of course considerably weakened. In the second place, the degree of interaction of the components with each other may be dissimilar. In other words, the negative deviations of the isotherms ε does not mean that only a breaking up of the associated molecules of the components occurs in the system, and not an interaction between the latter. In this case the negative deviations of the dielectric permeability from additivity give evidence of the fact that the polarity, in the case of chain association of the components, is considerably higher than the polarity in the case of complex formation. This is confirmed by studies of the electrical and optical properties of solutions of alcohols and phenols in such oxygen-containing solvents as nitrobenzene, ethers and others [18, 19]. Spectrographic studies also show that the nitro group is a weaker acceptor than the oxygen of ether and carbonyl.

In the methyl acetate -piperidine system whose dielectric permeability we studied at 10, 20, 30 and 40°, the negative deviations from additivity at all temperatures did not exceed 3%, which, apparently, is due to the considerable interaction between the carbonyl oxygen of the ester and the mobile hydrogen at the nitrogen of the piperidine.

The results of measurements of the dielectric permeability of the third group of systems are shown in Figs. 9-13 and in Table 3.

The data presented show that in all systems the isotherms of dielectric permeability have a positive deviation from the additive values, and in the following systems – chloroform-diethyl ether, quinoline-aniline, chloroform-methyl acetate, chloroform-benzyl acetate and chloroform-dibutyl ether, they pass through a maximum. The greatest deviations occur at concentrations corresponding to an equimolecular ratio of components. This becomes understandable if we take into consideration the fact that the reason for the increase in dielectric permeability is the chemical reaction between components with the formation of molecular aggregates and, consequently, the magnitude of the deviation must be proportional to the concentration of the aggregate formed. In a number of physical chemical studies it was shown that in some of the above-mentioned systems the components interact with one another with the formation of equimolecular aggregates [20, 21].

All this indicates that the classification of the isotherms of two-liquid systems and their interpretation from the point of view of the presence or absence of interaction between the components cannot be rational without calculating the properties of the micro particles of the components, in particular the polarity and character of their changes.

In conclusion we present the results of measurements of the dielectric permeability of the quinoline-chloroform system in benzene solution.

As can be seen from Fig. 14, as dilution with benzene increases, the magnitude of the deviation of the experimental isotherms of dielectric permeability from the additive values, and consequently, the degree of interaction between quinoline and chloroform decrease, and by the time 80 mol. % of benzene is reached, the isotherm becomes practically a straight line. We have presented this example in order to show that even at not very great dilutions, in the presence of a third component, it is sometimes impossible to detect interaction between the components of a binary system by the usual calculation of deviation from additivity.

SUMMARY

1. By means of measurements of the dielectric permeability of 23 two-liquid systems consisting of polar components it was shown that they may be divided into three groups on the basis of the shape of the isotherms.

2. Systems formed from components that do not react chemically and which have closely similar dipole moments have linear isotherms of dielectric permeability and this linearity is hardly affected by temperature changes.

3. Influence on the shape of the isotherms of dielectric permeability of two-liquid systems must result not only from reaction between components and dissociation of their molecules, but also from changes in polarity which may either increase or decrease during these processes. Therefore the sign of the deviation of the isotherms of dielectric permeability from additivity for systems consisting of polar components cannot serve as the sole criterion of the relation of the components to each other.

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POLAROGRAPHIC STUDIES OF SOME OXAZOLES

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Kharkhov Branch of the All-Union Scientific Research Institute of Chemical Reagents
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Derivatives of oxazole are widely used as luminophores in the preparation of scintillators [1-5]. The study of some properties of scintillators, such for example as aging resulting from various influences, requires rapid and objective methods of determining the concentration of luminophores. One of the methods of rapid quantitative analysis which is least dependent on other factors, is the polarographic method. However very few polarographic studies of five-membered rings have been published in the literature known to us; in particular, there is absolutely no data on the polarographic behavior of oxazole and its various derivatives. However the presence of conjugated bonds in the five-membered oxazole ring is the basis for suggesting the possibility of polarographic activity.

In the present paper some data are presented on a study of the polarographic properties of some phenyl-, diphenyl- and napthyl-substituted oxazoles 1,3 and the results obtained are also examined from the point of view of a connection between the polarographic properties and some optical properties.

EXPERIMENTAL

Methods of Procedure

The derivatives of oxazole that were studied were synthesized for the purpose of using them as luminophores in scintillators and were especially pure. The polarographic measurements were carried out on a Geirovskii-Shikat polarograph with an electrolyzer with an internal anode. The distance between the dropping electrode and the upper surface of the mercury at the bottom did not exceed 10 mm. The utilization of an internal anode resulted from the fact that a solution with a comparatively high specific resistance – a solution of $N(C_2H_5)_4I$, saturated at 20°, in 92% methanol – was used as a background. The introduction of an electrolytic bridge with a relatively small cross section (even when supplying it close to the dropping electrode) considerably increases the resistance between the cathode and the comparison anode in case it becomes filled with the same non-aqueous solution, while if the bridge is filled with an aqueous electrolyte it may contaminate the polarographic solution with water. The potential of the internal anode in comparison with the saturated calomel electrode is −0.285 v.

The original solutions of oxazole were prepared in mixtures consisting of 60% methanol and 40% dioxane. The methanol was freed from aldehydes by treatment with $AgNO_3$ in the presence of alkali and then distilled. Dioxane of "pure" grade was not further purified.

Results of the Study

The results of polarography showed that phenyl-, naphthyl- and biphenylyl-substituted oxazoles (background: $N(C_2H_5)_4I$ in 92% methanol) are reduced at the dropping mercury electrode and form polarographic waves (Figs. 1-7). The number of waves observed on the background mentioned, and the potential of the half-waves are different for different substituents. Thus, 2-methyl-5-phenyloxazole was not reduced at the dropping mercury electrode under the conditions we used. 2,5-Diphenyloxazole forms two waves on the polarogram with a potential of the half-wave of −2.10 v for the first wave and −2.33 v for the second against a saturated calomel electrode.

Replacement of a phenyl radical in position 2 by an α-naphthyl radical results in a shift of the first wave to −1.85 v. The introduction of a β-naphthyl radical in place of a phenyl radical causes the shift of $E_{1/2}$ of the first wave to be somewhat less than in the preceding case $E_{1/2} = -2.02$ v. $E_{1/2}$ of the second wave has a value of −2.23 v for the 1-naphthyl substituted and −2.23 v for the 2-naphthyl substituted, i.e., close to the value of the second wave of 2,5-diphenyloxazole. The introduction of the diphenyloxazolyl radical into position 2 has a large effect. In this case an even greater displacement of the first wave in the direction of less negative potentials is observed: $E_{1/2} = -1.77$v. The second wave has a value of $E_{1/2} = -2.18$ v, and the third wave $E_{1/2} = -2.38$ v.

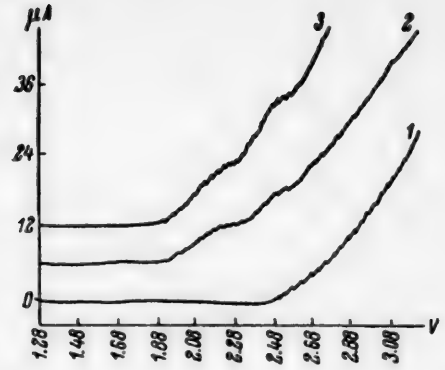


Fig. 1. Polarographic waves of 2,5-diphenyloxazole. 1) Background: $N(C_2H_5)_4I$ in 92% methanol; 2) 2,5-diphenyloxazole, 0.675 mmoles/liter; 3) same, 0.975 mmoles/liter.

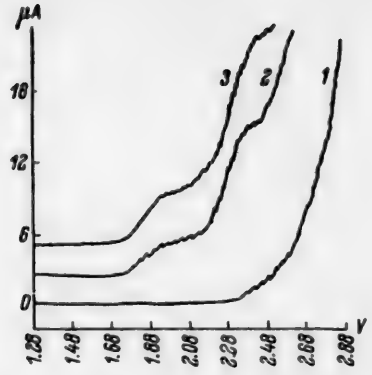


Fig. 2. Polarographic waves of 2-(1-naphthyl)-5-phenyloxazole. 1) Background: $N(C_2H_5)_4I$ in 92% methanol; 2) 2-(1-naphthyl)-5-phenyloxazole, 0.115 mmoles/liter; 3) same, 0.163 mmoles/liter.

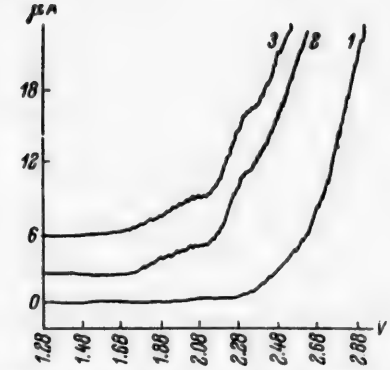


Fig. 3. Polarographic waves of 2-(2-naphthyl)-5-phenyloxazole. 1) Background: $N(C_2H_5)_4I$ in 92% methanol; 2) 2-(2-naphthyl)-5-phenyloxazole, 0.115 mmoles/liter; 3) same, 0.165 mmoles/liter.

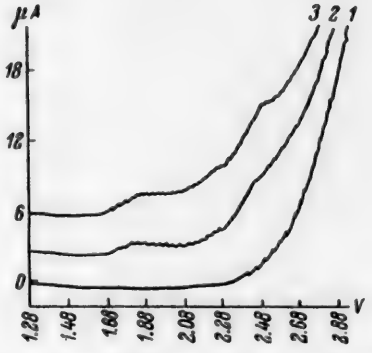


Fig. 4. Polarographic waves of 1,4-di(2-phenyloxazolyl)-benzene. 1) Background: $N(C_2H_5)_4I$ in 92% methanol; 2) 1,4-di(2-phenyloxazolyl)-benzene, 0.11 mmoles/liter; 3) same, 0.205 mmoles/liter.

This compound may be considered as consisting of two 5-phenyloxazole groups joined together by means of a phenyl radical which plays the role of a bridge in the electron interaction between the two groups.

If the $-CH = CH-$ group which contains easily mobile π-electrons is used as a bridge, the potential of the half-wave is strongly displaced toward positive values and becomes equal to -1.36 v. The introduction of the ethane group $-CH_2 = CH_2-$ instead of the $-CH = CH-$ as a bridge results in a loss of polarographic activity in 1,2-di(5-phenyloxazolyl)-ethane.

A study of influence of changes in the substituent in position 5 is also of interest. 2,5-Di(4-biphenylyl)-oxazole and 2-(4-biphenylyl)-5-(1-naphthyl)-oxazole were studied for this purpose. For the first substance two waves lying close together with $E^1_{1/2} = -2.00$ v and $E^2_{1/2} = -2.22$ v, and for the second substance $E^1_{1/2} = -1.97$ v and $E^2_{1/2} = -2.22$ v, i.e., the second waves of both substances coincide. In some cases these substances also show an indistinct third wave with a strongly negative potential.

Figure 8 shows the calibration curves for some of the substances studied which make it possible to determine oxazoles in solution quantitatively.

The Influence of Structure on the Polarographic Properties of Oxazoles and Its Relation to Some Optical Properties

It follows from the experimental data presented that the five-membered oxazole ring is capable of being reduced under certain conditions at the mercury dropping electrode and that the ease of its reduction is considerably influenced by its substituents. Substituents in position 2 have especially marked influence. Thus, for example, the introduction

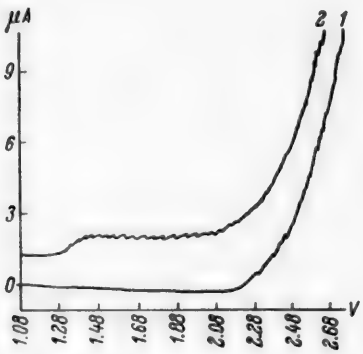


Fig. 5. Polarographic waves of 1,2-di(2-phenyloxazolyl)-ethylene. 1) Background: $N(C_2H_5)_4I$ in 92% methanol; 2) 1,2-di(2-phenyloxazolyl)- ethylene, 0.305 mmoles/liter.

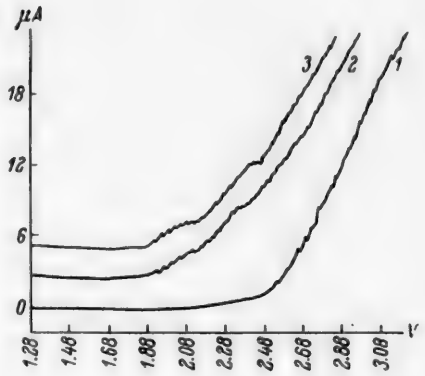


Fig. 6. Polarographic waves of 2,5-di(4-biphenylyl)-oxazole. 1) Background: $N(C_2H_5)_4I$ in 92% methanol; 2) 2,5-di(4-biphenylyl)-oxazole, 0.091 mmoles/liter; 3) same, 0.107 mmoles/liter.

of a phenyl radical into position 2 in place of a methyl radical causes the appearance of polarographic waves, and their potential changes considerably with changes in the nature of the substituents. Substituents in position 5 apparently have less influence since replacement of the biphenyl radical in position 5 by the 1-naphthyl radical, while keeping the substituent in position 2 unchanged, had little influence on the potential of the half-wave for the first wave.

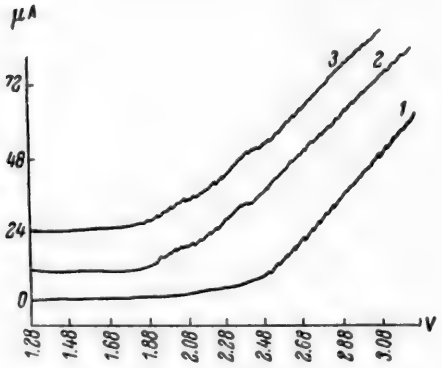


Fig. 7. Polarographic waves of 2-(4-biphenylyl)-5-(1-naphthyl)-oxazole. 1) Background: $N(C_2H_5)_4I$ in 92% methanol; 2) 2-(4-biphenylyl)-5-(1-naphthyl)-oxazole, 0.620 mmoles/liter; 3) same, 0.965 mmoles/liter.

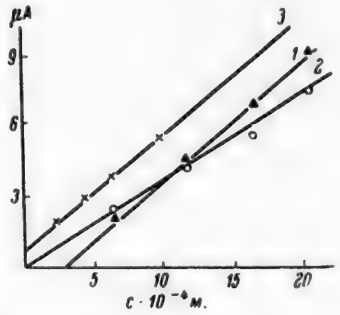
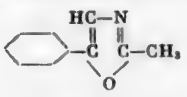
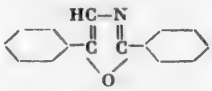
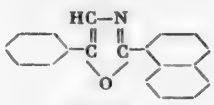
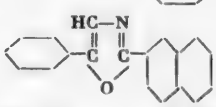
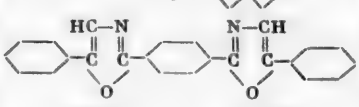
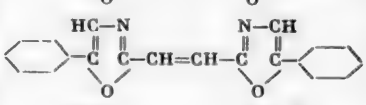
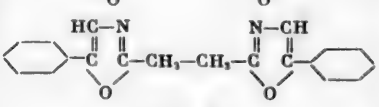
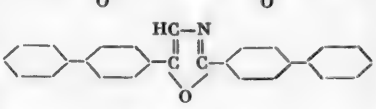
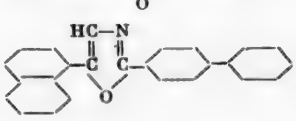


Fig. 8. Calibrating curves on the background of $N(C_2H_5)_4I$ in 92% methanol. 1) 2-(1-naphthyl)-5-phenyloxazole; 2) 2-(2-naphthyl)-5-phenyloxazole; 3) 2-(4-biphenylyl)-5-(1-naphthyl)-oxazole.

These results indicate that the most easily reduced bond is apparently $>C=N-$, the reduction of which evidently occurs first. Since after reduction of this double bond, the link between the substituents in position 2 and the $>C=C<$ bond (between carbons 4 and 5) is broken, this substituent has no actual influence on the $E_{1/2}$ of the

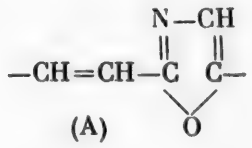
Optical and Electrochemical Characteristics of Oxazole Derivatives

No.	Formula	λ_{max} of absorption in heptane (mμ)	λ of luminescence in polystyrene (mμ)	I of scintillation in polystrene* (%)	$E_{1/2}$ (V)
1		275	—	—	Not reduced
2		310	380	100	—2.10, —2.33
3		325 (335)	415	116	—1.85, —2.23
4		320 (330)	405	125	—2.02, —2.23
5		335	425	114	—1.77, —2.18, —2.38
6		283	—	—	—1.36
7		275	—	—	Not reduced
8		—	415	135	—2.00, —2.22
9		348	425	140	—1.97, —2.22

* Relative to 2,5-diphenyloxazole, whose value of I_{sc} is taken as 100%.

second wave. In this connection, the potentials of the half-waves of the second waves for substances 2, 3 and 4 (see table) are close in value. Attention is called to the fact that the substitution of aromatic radicals by alkyl radicals in position 2 makes the $>C=N-$ bond incapable of reduction, and in this connection 2-methyl-5-phenyloxazole and 1,2-di(5-phenyloxazole)-ethane are not reduced at the dropping mercury electrode.

The electronegative effect of aromatic radicals joined to the $>C=N-$ bond is apparently connected in the first place with a lengthening of the chain of conjugated double bonds. This conclusion is also confirmed by the introduction of radical (A) with a system of conjugated double bonds into position 2: 1,2-di(5-phenyloxazolyl)-ethylene is still more easily reduced than when aromatic radicals are present in position 2. The latter are apparently to a certain degree withdrawn from coplanarity in relation to the plane of the oxazole ring.

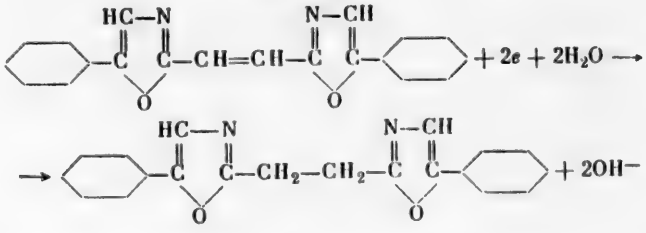


(A)

It should also be noted that in contrast to all other oxazole derivatives studied by us, the last compound (table, No. 6) is not reduced at the $>C=N-$ bond, but at the $-CH=CH-$ bond. As was shown by our microcoulombmetric studies, the number of electrons n taking part in the reduction of one molecule of this compound is 2.

Thus the electrochemical reaction at the dropping mercury electrode for 1,2-di(5-phenyloxazolyl)-ethylene may be shown as follows.

First wave



This mechanism is confirmed by the fact that when $-CH=CH-$ is reduced it is changed into $-CH_2=CH_2-$, i.e., 1,2-di(5-phenyloxazolyl)-ethylene is converted into 1,2-di(5-phenyloxazolyl)-ethane which, as can be seen from the data in the tables, does not give polarographic waves. Consequently after the first reduction wave of 1,2-di(5-phenyloxazolyl)-ethylene, no other waves are observed as there are in the case of 1,2-di(5-phenyloxazolyl)-ethane.

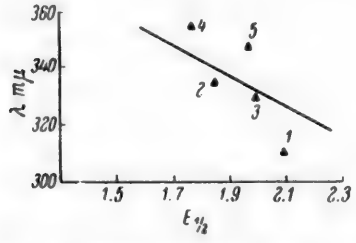


Fig. 9. Results of comparing $E_{1/2}$ and λ_{max} of absorption in heptane. 1) 2,5-diphenyloxazole; 2) 2-(1-naphthyl)-5-phenyloxazole; 3) 2-(2-naphthyl)-5-phenyloxazole; 4) 1,2-di(2-phenyloxazolyl)-benzene; 5) 2-(4-biphenylyl)-5-(1-naphthyl)-oxazole.

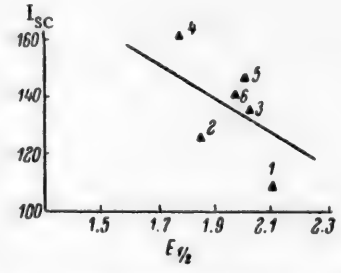


Fig. 10. Results of comparing $E_{1/2}$ with scintillation effectiveness. 1) 2,5-diphenyloxazole; 2) 2-(1-naphthyl)-5-phenyloxazole; 3) 2-(2-naphthyl)-5-phenyloxazole; 4) 1,4-di(2-phenyloxazolyl)-benzene; 5) 2,5-di(4-biphenylyl)-oxazole; 6) 2-(4-biphenylyl)-5-(1-naphthyl)-oxazole.

The table also shows the lengths of the waves at the peaks of the absorption spectra of the substances studied (Fig. 9). The changes of λ_{max} in general also correspond with changes in the value of $E_{1/2}$, which confirms the dependence of the polarographic properties of the series of compounds studied on the character of the substituent.

Inasmuch as there is a definite interrelationship between the optical properties and effectiveness of scintillation, the determination of this connection with polarographic properties is of definite interest. We have compared the scintillation properties of the oxazoles studied with the values of the half-wave potentials (Fig. 10). From the figure it is evident that there is a definite correlation between these properties.

These results indicate that the polarographic method may be used for an orienting determination of the possibility of using a given substance as an effective scintillator, since substances with a larger positive half-wave potential must correspond with a higher scintillation effectiveness. This circumstance makes it possible to show the degree of purity of the compound.

SUMMARY

1. Studies on the polarographic activity of some phenyl-, biphenylyl- and naphthyl substituted oxazoles were carried out, and their basic polarographic properties determined. The polarographic activity of the oxazoles studied was examined from the point of view of the influence of substituents.

2. The polarographic data obtained were compared with the absorption spectra and scintillation effectiveness of plastic scintillators containing the substances studied as scintillating admixtures. In this connection, a definite correlation between $E_{1/2}$ and scintillation effectiveness was found for the first time.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

A STUDY OF THE MECHANISM OF OXIDATION OF ALDEHYDES BY OXYGEN IN AQUEOUS SOLUTION AND OF ISOTOPIC EXCHANGE OF SUBSTITUTED BENZALDEHYDES WITH H_2O^{18}

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pp. 3167-3170, October, 1961
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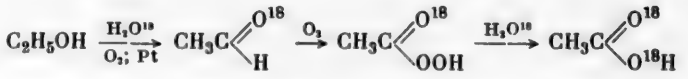
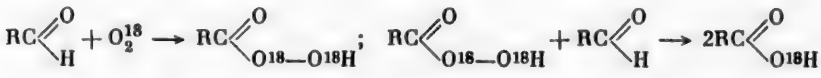
Rottenberg and his co-workers [1] studied the oxidation of an aqueous solution of ethyl alcohol in the presence of platinized carbon with the aid of O^{18} and found that the oxygen in the resulting acetic acid came principally from the water and not from the gas phase. As one of the possible reaction schemes these authors suggested that the acetaldehyde formed by oxidation rapidly exchanges oxygen with the water and is oxidized to a per acid which then hydrolyzes to acetic acid.



(1)

Another example of an analogous reaction was found by Bentley and Neuberger [2] who showed that when oxygen acts on an aqueous solution of glucopyranose in the presence of the ferment notatine, gluconic acid is formed which also does not contain oxygen from the gas phase. They explained this result by suggesting that the reaction proceeds by a dehydrogenation mechanism.

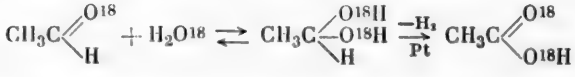
The results of these studies do not agree with the usual view on the mechanism of aldehyde oxidation [3], in accordance with which the reaction proceeds with the intermediate formation of a per acid which then oxidizes a molecule of aldehyde, since such a course of the reaction would lead to the transition of one atom of oxygen from the gas phase into the acid.



(2)

Keeping this contradiction in mind, in the present study we investigated the oxidation of several aldehydes by heavy oxygen in ordinary water, or by ordinary oxygen in H_2O^{18}. The system was homogeneous in the case of acetaldehyde and heterogeneous for other aldehydes. The reaction was carried out at room temperature both in the presence of platinized carbon and without a catalyst. The results of the experiments are shown in Table 1.

These data show that both in the presence and in the absence of a catalyst, the aldehydes studied gain one atom of oxygen from the gas on oxidation, which agrees with the usual scheme (2). In accordance with the data of Rottenberg and his co-workers, the only exception was the oxidation of acetaldehyde catalyzed by platinized carbon, where the oxygen of the acid comes only from the water. The mechanism of this reaction, in addition to scheme (1), may be considered as a dehydrogenation of the hydrate form of the aldehyde.



(3)

It was mentioned above that such a mechanism, previously proposed by Wieland [4], had been suggested for the oxidation of glucopyranose in the presence of notatine. In this connection it is interesting to note that the rate of oxidation of acetaldehyde by oxygen on palladium, and the rate of isotopic exchange of the oxygen of the aldehyde with water, is of the same order [5].

TABLE 1. Distribution of O^{18} in Oxidizing Aldehydes

No.	Aldehyde	Quantity (in g)			Length of oxidation	Excess content of O^{18} (in atom %)				
						in original			found in resulting acid	calculated for the transfer of 1 atom of oxygen from the gas phase to the acid
		aldehyde	water	platinized carbon		aldehyde	water	oxygen		
1	o-Chlorobenzaldehyde	1.28	1.00	–	6 days	0	0	1.07	0.48	0.53
2	The same	0.43	0.35	–	2 days	1.19	1.19	0	0.56	0.59
3	The same	0.78	2.00	0.075	6 hours	0	0	1.07	0.51	0.53
4	Benzaldehyde	0.80	4.00	–	15 hours	0	0	1.07	0.49	0.53
5	Acetaldehyde	0.50	1.00	–	20 days	0.93	0.93	0	0.37	0.46
6	The same*	0.9	10.00	0.035	9 hours	0	0	1.07	0	0.53
7	Butyraldehyde	0.58	4.32	–	2 days	1.11	1.11	0	0.53	0.55
8	The same	0.86	5.01	0.100	2 days	1.12	1.12	0	0.42	0.56
9	The same	2.60	10.0	0.200	9 hours	0	0	1.07	0.40	0.53

* The oxidation was carried out at 70°.

In addition to a study of oxidation, we also studied the isotopic exchange of oxygen in a series of substituted benzaldehydes with heavy-oxygen water H_2O^{18} in a dioxane-water solution.* The results obtained are interesting in view of the absence of systematic studies of the isotopic exchange of the oxygen of aldehydes in relation to their structure.

Results of the experiments are given in Table 2. They are only approximate because of difficulties we encountered in isotope analysis of the oxygen of the aldehydes. The data of Table 2, however, reliably show some regularities which affect a change in the rate of exchange by several orders of magnitude. Isotopic exchange is catalyzed by acid: in the presence of HCl all the compounds studied rapidly exchange oxygen even at room temperature or a little higher. Aldehydes with electron donor substituents [OH, OCH_3, OCH_2O, $N(CH_3)_2$] exchange oxygen considerably more slowly than aldehydes with electron acceptor substituents (NO_2, Cl, $C\begin{matrix}O\\ \diagup\\ \diagdown\\ H\end{matrix}$) These regularities show that exchange, like many other reactions of aldehydes, is a nucleophilic reaction and is most probably a reversible hydration [6] which is facilitated by drawing electrons from the carbonyl group and linking a proton to it, as Cohn and Urey suggested previously [7]. An analogous exchange mechanism for the oxygen of inorganic acids and salts through intermediate hydration was proposed by Brodskii and his co-workers [8].

EXPERIMENTAL

Starting compounds. Aldehydes labeled with O^{18} for experiments 2, 5, 7, and 8 (Table 1) were prepared by isotope exchange with heavy-oxygen water at 100° for 50 hours. During this period isotopic equilibrium was attained and aldehydes and water with an equal content of O^{18} were used in the experiments. Platinized carbon was prepared according to method [9] and contained 10% of platinum. The dioxane was carefully purified and dehydrated [10]. The heavy-oxygen water was purified by prolonged boiling with $KMnO_4$ in an acid and alkaline medium, distilled three times in a quartz apparatus and kept in a quartz container.

Oxidation of the aldehydes was accomplished by shaking with water and catalyst in an atmosphere of oxygen. Barium carbonate was added to the reaction mixture in experiments 5-9 (Table 1) until the oxidation began, and the

* Control experiments showed that dioxane does not exchange its oxygen with H_2O^{18} in an acid or alkaline medium during a five hour period at 100°.

TABLE 2. Exchange of Substituted Benzaldehydes with H_2O^{18}

No.	Aldehyde	Quantity (in g)			Catalyst HCl	Temperature	Length of exchange (hours)	Excess content of O^{18} in the carbonyl group (in atom %)		Percent exchange
		aldehyde	H_2O^{18}*	dioxane				found	calculated for equilibrium	
1	Benzaldehyde [6]	6	1.5	—	—	25°	20	—	—	85
2	o-Chlorobenzaldehyde	0.19	0.21	2	—	60	3	0.27	1.10	25
3	The same	0.37	0.38	4	0.1 N	10	<0.1**	0.35	1.04	35
4	o-Nitrobenzaldehyde	0.50	0.50	2	—	20	24	0.69	0.98	70
5	The same	0.19	0.18	2	0.1 N	20	1	1.02	0.93	>100
6	p-Nitrobenzaldehyde	0.46	0.50	5	—	20	24	0.75	0.93	80
7	The same	0.19	0.18	2	0.1 N	20	1	0.77	0.86	90
8	m-Nitrobenzaldehyde	0.45	0.50	2	—	20	24	0.52	1.01	50
9	The same	0.19	0.18	2	0.1 N	10	<0.1**	0.56	1.09	50
10	Salicylaldehyde	0.65	0.80	8	—	70	6	0.14	1.11	10
11	The same	0.32	0.38	4	0.1 N	40	3	0.65	1.04	65
12	Anisaldehyde	0.72	0.80	8	—	70	6	0.15	1.10	15
13	The same	0.36	0.38	4	0.1 N	40	3	0.44	1.06	40
14	p-Hydroxybenzaldehyde	0.16	0.20	2	—	70	6	0.27	1.11	25
15	The same	0.16	0.19	2	0.1 N	40	3	0.48	1.04	45
16	Heliotropin	0.20	0.20	2	—	70	6	0.002	1.11	0
17	The same	0.20	0.19	2	0.1 N	40	3	0.30	1.04	30
18	p-Dimethylaminobenzaldehyde	0.19	0.20	2	—	50	15	0.003	1.11	0
19	The same	0.45	0.48	1.5	0.25 N	20	23	0.24	0.94	25
20	The same	0.45	0.86	1.5	0.4 N	20	24	0.52	0.98	55
21	Isophthalic aldehyde	0.19	0.20	2	—	60	3	0.14	0.86	15

* The excess content of O^{18} in the original water was 1.12 atom % in experiments without acid, and 1.05 atom % in experiments with acid. In experiments 1, 2, 11, 13, 14, 15, 16, the excess of O^{18} was equal to 1.24 and 1.17 atom % respectively.

** Separation was begun immediately after mixing and lasted for several minutes.

acids formed were separated as solutions of their barium salts. These solutions were extracted three times with benzene, evaporated in vacuo, and the salts dried to constant weight in a high vacuum at 100°. In experiments 1-4 the acids were separated as the sodium salts by the addition of soda to the reaction mixture after oxidation. The solutions of the salts were washed three times with benzene and the organic acid separated by means of hydrochloric acid and dried.

In experiments 5-9 the acetate and butyrate of barium, and in experiments 1-4 benzoic and chlorobenzoic acids were subjected to isotopic analysis. Their melting points corresponded with the values in the literature. It was shown by special control experiments that these compounds do not exchange oxygen with H_2O^{18} under the oxidation conditions for aldehydes.

Isotopic exchange of aldehydes. A homogeneous mixture of aldehydes, dioxane and water (or acidified water) was maintained for a fixed time in a thermostat in sealed glass ampoules. Then the dioxane and water were distilled off in the course of a few minutes in vacuo at room temperature, and the compounds were purified by sublimation or distillation in vacuo. Their melting points and refractions corresponded with the data in the literature. These compounds were subjected to isotopic analysis.

Isotopic analysis. For isotopic analysis, organic compounds were cracked in quartz or platinum ampoules in the presence of a given quantity of carbon dioxide of normal isotopic composition and the CO_2, having reached an equi-

librium content of O^{18} was analyzed in a mass spectrometer [11]. In the case of barium butyrate, the analytical results were lowered because of mixing with CO_2 formed by cracking of the hydrocarbons (experiments 8 and 9, Table 1). The analysis of aldehydes was also imprecise (in the case of o-chlorobenzaldehyde, p-dimethylaminobenzaldehyde and isophthalic aldehyde the error amounted to as much as 10%, while in the case of nitro-, hydroxy- and alkoxy benzaldehydes it amounted to as much as 25%) apparently because of incomplete cracking which distorted the results when various functional groups containing oxygen were present in the molecule.

We wish to express our thanks to A. I. Brodskii for his constant interest in this work and his discussion of the results.

SUMMARY

1. On oxidizing acetaldehyde, butyraldehyde, benzaldehyde and o-chlorobenzaldehyde with oxygen in an aqueous medium, one atom of oxygen from the gas phase enters the acid which is formed. The same phenomenon is observed in the catalytic oxidation in the presence of platinized carbon of all aldehydes, except acetaldehyde, which in this case gives an acid whose oxygen comes only from the water.

2. Isotopic exchange of oxygen between substituted benzaldehydes and H_2O^{18} is catalyzed by acid. Aldehydes with electron acceptor substituents exchange oxygen considerably more rapidly than aldehydes with electron donor substituents. These facts indicate a nucleophilic mechanism for the exchange reaction and are in agreement with the hypothesis of an intermediate hydration stage.

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THE ACTIVATION ENERGY OF THE REACTION OF CHAIN GROWTH DURING THE OXIDATION OF ISOPROPYLBENZENE AND 1,1-DIPHENYLETHANE

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Investigation of the mechanism of the complex chain oxidation reaction of hydrocarbons requires the determination of the fundamental kinetic characteristics of the individual elementary parts of the reaction. At the present time the rate constants and their dependence on temperature for the reactions of growth, branching and breaking of the chains are basically known for only a small number of olefins and some of their derivatives [1, 2]. With few exceptions, similar information is lacking on the oxidation reactions of many aliphatic and alkylaromatic hydrocarbons. A study of the oxidation of these hydrocarbons is often of great practical importance. The present paper gives the results of the determination of the activation energy of chain growth and degenerate branching during the oxidation of isopropylbenzene and 1,1-diphenylethane – hydrocarbons whose oxidative treatment is carried out on an industrial scale. Fundamental to the study is the method of calculating the activation energy of chain growth on the basis of data on the kinetics of oxidation of hydrocarbons.

The mechanism of formation of hydroperoxides – the only product at the beginning of the reaction – may be indicated by the following chain scheme:

$$R^{\cdot} + O_2 \longrightarrow ROO^{\cdot}$$
$$ROO^{\cdot} + RH \longrightarrow ROOH + R^{\cdot}$$

The rate of formation of hydroperoxides during the initial period is described by the equation

$$\frac{d[ROOH]}{dt} = \frac{k_1[RH]}{k_2^{1/2}} w_{init}^{1/2} \quad (1)$$

where k_1 is the rate constant for the growth of the chain, k_2 is the rate constant for chain breaking, w_{init} is the rate of initiation of the chain reaction and is equal to the sum of the rate of spontaneous appearance of active particles (w_0) and the rate of degenerate branching ($k_3[ROOH]$). If we assume that active particles spontaneously appear as a result of the reaction

$$RH + O_2 \longrightarrow R^{\cdot} + HO_2^{\cdot},$$

then

$$w_0 = k_0[RH][O_2].$$

Approximate evaluation of the magnitude of w_0 shows that even in the early stages the rate of degenerate branching is larger than w_0 and, consequently, equation (1) may be rewritten as

$$\frac{d[ROOH]}{dt} = \frac{k_1[RH]}{k_2^{1/2}} (k_3[ROOH])^{1/2}.$$

From this relationship an equation for the total activation energy E may be obtained, which is determined from the initial parts of the kinetic curves:

$$E = E_1 - 0.5E_2 + 0.5E_3,$$

where E_1, E_2, and E_3 are the activation energies of the reactions of growth, breaking and degenerate branching respectively.

The value of E_3 for isopropylbenzene, according to the literature, is equal to 30.4 kcal/mole [3]. The value of E_3 for 1,1-diphenylethane is unknown. Usually the rate constant for the decomposition of hydroperoxides depends on the initial concentration [3, 4]. In this case, if an equation of the first order is being carried out, the value of the rate constant of the initiation reaction used is that obtained from an extrapolation of the dependence of the rate constant of decomposition on the initial hydroperoxide concentration to the null value of the concentration. We used this method to calculate the values of K_3 and E_3 for 1,1-diphenylethane.

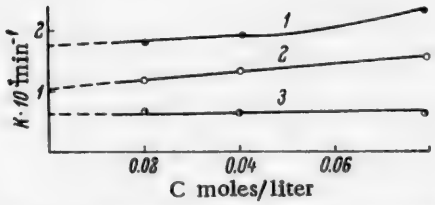

Fig. 1. Dependence of the rate constant of decomposition of the hydroperoxide of 1,1-diphenylethane on concentration at 130° (1), 120° (2), and 110° (3).

Study of the decomposition of hydroperoxide of 1,1-diphenylethane was carried out in an atmosphere of pure nitrogen. The dependence of the rate constant of decomposition on the initial hydroperoxide concentration is shown in Fig. 1. The values of k_3 (the true constant of monomolecular decomposition) made it possible to calculate E_3 and the magnitude of the pre-exponential factor in the Arrhenius equation. The dependence of the true rate constant of decomposition on temperature, therefore, is described by the equation

$$k = 0.803 \cdot 10^6 \cdot \exp(-16000/RT) \cdot \text{sec}^{-1} \qquad (2)$$

Attention should be called to the low energy of activation of the process and to the low pre-exponential factor.

Isopropyl benzene and 1,1-diphenylethane, synthesized according to method [8], were used for the oxidation. Before being used in the experiments the hydrocarbons were carefully purified by repeated shaking with sulfuric acid, with a 10% solution of caustic soda, then washed with water, shaken several times with a 1% solution of $KMnO_4$, washed once again with water, dried over metallic sodium and finally distilled. The constants of isopropylbenzene and 1,1-diphenylethane corresponded with those in the literature.

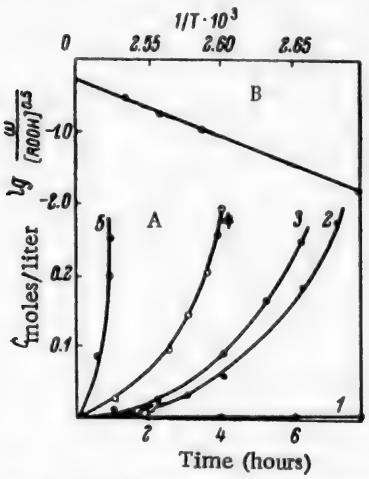

Fig. 2. A) Kinetic curves of the accumulation of hydroperoxide during the oxidation of isopropylbenzene at 100° (1), 109° (2), 115° (3), 123.5° (4), 130° (5); B) dependence of $\log(w \cdot [ROOH]^{-1/2}) = f(T^{-1})$.

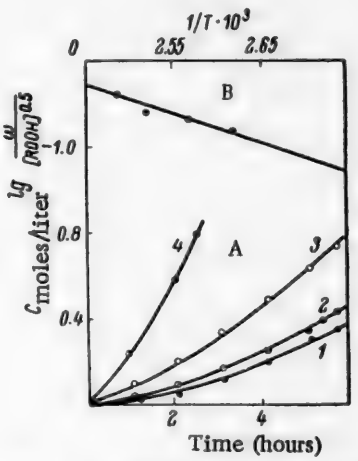

Fig. 3. A) Kinetic curves of the accumulation of hydroperoxides during the oxidation of 1,1-diphenylethane at 109° (1), 115° (2), 123.5° (3), 130° (4); B) dependence of $\log(w \cdot [ROOH]^{-1/2}) = f(T^{-1})$.

The experiments on the oxidation of isopropylbenzene and 1,1-diphenylethane were carried out in the usual glass vessel with a reflux condenser and a porous partition through which dispersed oxygen was passed. The experiments were completely reproducible. The kinetic curves of hydroperoxide accumulation are shown in Figs. 2 and 3.

On the basis of the kinetic data it is possible to calculate the magnitude of the ratio $k_1 k_3^{-1/2}$ [RH] for various temperatures which in turn permits the calculation of the activation energy of the gross process. The dependence of the logarithm of the product of the constants on the magnitude of the reciprocal temperature is shown in Figs. 2C and 3C. The calculated energies of activation of the gross processes were found to be equal to 23.8 kcal for isopropylbenzene and 14 kcal for 1,1-diphenylethane, which corresponds with the values of E_1, which were found to be 8.6 kcal/mole and 6 kcal/mole respectively ($E_2 \approx 0$). Calculation of the activation energy of the reaction of chain growth according to the Polyani equation for isopropylbenzene gives a value of 7.5kcal (q_{C-H} 74 kcal q_{ROO-H} 90 kcal), which agrees satisfactorily with the values obtained experimentally. The energy of the C – H bond in 1,1-diphenylethane is unknown. Phenyl groups in contrast to methyl groups have a negative induction effect. Therefore replacement of the CH_3 group by C_6H_5 must lead to an appreciable weakening of the C – H bond. As a matter of fact, the energy of the C – H bond at the tertiary carbon atom in the isobutane molecule is equal to 85 kcal, while in the isopropylbenzene molecule it is 74 kcal[5]. Replacement of the methyl group by a phenyl group (in 1,1-diphenylethane) must still further weaken the C – H bond at the tertiary carbon atom. If it is assumed that substitution of the methyl group by a phenyl group decreases the energy of the C – H bond by approximately 10 kcal and also that q_{C-H} for 1,1-diphenylethane is 64 kcal then the value of E_2, calculated in accordance with the Polyani equation, will be 5 kcal i.e., a value close to that found experimentally. If we take into consideration the fact that the value of the energy of the bond in isobutane, which is equal to 85 kcal is apparently somewhat overstated, it must be acknowledge that the values obtained for the activation energies are good. The coincidence of the experimental values with those calculated according to the Polyani equation serves as indirect confirmation of the probability of an anomalously low value for the activation energy of the decomposition of the hydroperoxide of 1,1-diphenylethane. Further evidence for this is obtained from a comparison of the values of the energies of activation of the decomposition reaction of tertiary butyl and isopropyl benzene, and also data obtained by Yurenko and co-workers on the decomposition of the hydroperoxide of 1,1-diphenylethane in methylstyrene [6].

Hydroperoxide	Decomposition rate constant (sec^{-1})
Tertiary butyl	$1.2 \cdot 10^{15} \cdot e^{-39000/RT}$
Isopropylbenzene	$2{,}7 \cdot 10^{12} \cdot e^{-30400/RT}$
1,1-Diphenylethane	$0{,}8 \cdot 10^{6} \cdot e^{-15000/RT}$

Attention should be called to fact that in passing from tertiary butyl hydroperoxide to the hydroperoxide of 1,1-diphenylethane, there is not only a decrease in the activation energy of the decomposition process, but also a large decrease in the pre-exponential factor. The normal value of the pre-exponent for monomolecular reactions of one order with an average vibration frequency at the ruptured bond is $10^{12}-10^{14}$ sec^{-1}. The abonormally low value of the pre-exponent for the decomposition of the hydroperoxide of 1,1-diphenylethane may be explained, apparently, by the following circumstance. It has recently been discovered [7] that the decomposition of hydroperoxides in a hydrocarbon medium may proceed both as a monomolecular reaction – for example, according to the equation

$$ROOH \longrightarrow RO^{\cdot} + HO^{\cdot},$$

and as a result of a bimolecular reaction with hydrocarbon

$$ROOH + RH \longrightarrow RO^{\cdot} + R^{\cdot} + H_2O.$$

The less stable the C – H bond in the hydrocarbon, the greater the importance of the latter reaction in the over-all balance. Thus, the values of k_3 obtained by extrapolation and the calculated activation energies (E_3) must be regarded as effective magnitudes characteristic of the over-all rate of the oxidation process.

In this case the pre-exponential factors naturally may have values within broad limits.

SUMMARY

1. The dependence of the rate of oxidation of isopropylbenzene and 1,1-diphenylethane on temperature was studied. The calculated activation energy of the elementary act of chain growth was found to be equal to 8.6 kcal/mole for isopropylbenzene, and to 6.0 kcal/ mole for 1,1-diphenylethane.

2. The hypothesis was stated that the decomposition of the hydroperoxide of 1,1-diphenylethane in a hydrocarbon medium proceeds in considerable measure as a bimolecular reaction of the hydroperoxide with the hydrocarbon.

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THE TRANSESTERIFICATION OF THIOLPHOSPHINITES AND THIOLPHOSPHONATES BY ALCOHOLS

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It is known that acid and neutral esters of trivalent phosphorus acids and also esters of carboxylic acids, are easily transesterified by alcohols. We studied this reaction using as examples the transesterification of phosphinites by monatomic alcohols, glycols and derivatives of glycerine [1-3]. The amides of trivalent phosphorus acids, like the esters, also easily undergo alcoholysis with the formation of the corresponding phosphinites, as we have previously shown [4]. Neutral phosphates and phosphonates, in contrast to the phosphites, react with alcohols only with great difficulty [5, 6]. Consequently the transesterification of esters of pentavalent phosphorus acids has not become significant as a preparative method.

In this research we studied the alcoholysis of thiophosphinites and phosphonates for the purpose of finding new methods of synthesizing the esters of trivalent and pentavalent phosphorus acids. It was assumed that this reaction would proceed in the desired direction by analogy with the thiol esters of carboxylic acids, which are transesterified considerably more easily than their oxygen analogs. Experiments showed that dithioethylmethylphosphinite reacts both with primary and secondary alcohols to form esters of methylphosphinous acid.

$$CH_3—P(SC_2H_5)_2 + 2ROH \longrightarrow CH_3—P(OR)_2 + 2C_2H_5SH$$

The yield of phosphinites did not exceed 25-50% and was lower than in the case of the transesterification of the acid esters of phosphinous acid. This is apparently explained by the fact that during the course of the reaction the mercaptan formed and its oxidation product – disulfide – react with phosphinite and form a motley mixture of substances [7, 8]. The esters of methylphosphinous acid obtained by this method, and which have not been described in the literature, are shown in Table 1.

The dithiol esters of methylphosphinic acid, unlike the phosphates and phosphonates, are easily transesterified by alcohols and form neutral esters in good yield.

$$CH_3—\underset{\underset{O}{\|}}{P}\!\!<\!\!\begin{matrix}SC_2H_5\\SC_2H_5\end{matrix} + 2ROH \longrightarrow CH_3—\underset{\underset{O}{\|}}{P}\!\!<\!\!\begin{matrix}OR\\OR\end{matrix} + 2C_2H_5SH$$

Alcoholysis by means of primary alcohols proceeds considerably more easily than with secondary alcohols. When the reaction was carried out with tertiary alcohols, it was not possible to separate the phosphonate individually. It must be assumed that the compound sought was severely contaminated by a non-symmetrical product of monotransesterification $CH_3 – PO(SC_2H_5)(OR)$. The constants are shown in Table 2.

The transesterification reaction is of a general character in the sense that it proceeds not only with monatomic alcohols, but also with glycols. Thus, on heating dithioethylmethylphosphonate with glycol, a polymer is obtained which cannot be distilled even under a high vacuum and is apparently a polyphosphonate.*

$$n\,CH_3—\underset{\underset{O}{\|}}{P}(SC_2H_5)_2 + n\,HOCH_2CH_2OH \xrightarrow{-2n\ C_2H_5SH} \left[—OCH_2CH_2—O—\underset{\underset{O}{\|}}{\overset{\overset{CH_3}{|}}{P}}—OCH_2CH_2—O—\right]_n$$

* We shall look more carefully into the synthesis of polymeric compounds by means of the thiolphosphonate reaction with glycols later on.

TABLE 1. Transesterification of the Dithiol Ester of Methylphosphinous Acid

No.	Quantity of original thiolphosphinite (in g)	Alcohol	Quantity of alcohol (in g)	Temperature	Yield, %	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Empirical formula	% P found	% P calculated
1	6.64	$C_6H_{13}OH$	8.18	160—180°	44.2	129—133° (8)	1.4454	0.9404	70.33	69.74	$C_{13}H_{29}O_2P$	12.58, 12.66	12.47
2	5.05	$C_8H_{17}OH$	7.8	155—180	37.5	128—135 (1)	1.4582	0.9333	89.03	90.11	$C_{17}H_{37}O_2P$	10.28, 10.33	10.18
3	5.05	sec-$C_8H_{17}OH$	7.8	160—180	24.2	110—115 (1)	1.4618	0.9386	89.13	90.11	$C_{17}H_{37}O_2P$	10.92, 10.75	10.18
4	6.64	Cyclohexanol	8.0	160—180	54.8	145—150 (12)	1.4480	0.9461	69.12	65.34	$C_{13}H_{25}O_2P$	12.73, 12.61	12.71

TABLE 2. Transesterification of the Diethyl Ester of Methylphosphinic Acid

No.	Quantity of original thiolphosphinite (in g)	Alcohol	Temperature	Yield, %	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Empirical formula	% P found	% P calculated
1	5.52	C_4H_9OH 6.66	130—160°	76.5	132—135° (15)	1.4240	0.9470	56.10	54.63	$C_9H_{21}O_3P$	14.70, 14.96	14.82
2	6.42	$C_6H_{13}OH$ 10.7	170—190	74.0	137—140 (2)	1.4367	0.9448	71.58	71.20	$C_{13}H_{29}O_3P$	12.03, 12.10	11.72
3	4.6	$C_8H_{17}OH$ 9.75	180—200	50.0	137—140 (0.5)	1.4452	0.9229	92.43	91.57	$C_{17}H_{37}O_3P$	9.43, 9.32	9.66
4	4.6	sec.-$C_8H_{17}OH$ 9.75	180—200	17.5	78—83 (1)	1.4525	0.9035	95.76	91.57	$C_{17}H_{37}O_3P$	9.91, 9.95	9.66

The diethyl esters of methylphosphinous and methylphosphinic acids, previously unknown, were obtained by us reacting the corresponding acid chlorides with sodium mercaptide.

$$CH_3PCl_2 \xrightarrow{NaSC_2H_5} CH_3P(SC_2H_5)_2 \xrightarrow{N_2O_4} CH_3P(SC_2H_5)_2$$

$$CH_3P(O)Cl_2 \xrightarrow{NaSC_2H_5} CH_3P(O)(SC_2H_5)_2$$

The structure of the dithiol esters obtained was demonstrated by oxidizing dithiolphosphinite to the corresponding phosphonate which was found to be identical with the dithiolphosphonate obtained by the method mentioned above.

Thus the present study has shown that thiolphosphinites and phosphonates undergo transesterification with alcohols, and in contrast to the corresponding oxygen derivatives the thiol esters of phosphinic acid undergo alcoholysis better than the esters of phosphinous acid.

EXPERIMENTAL

1. The dithioethyl ester of methylphosphinous acid. 11.5 g of metallic sodium was gradually added in small portions and allowed to dissolve in 150 ml of liquid ammonia containing 30.5 g of diethyldisulfide. Then 120 ml of absolute ether was carefully added to the reaction mixture. The ammonia was driven off after heating the mixture to 30-35°. After removal of the ammonia, a solution of 29.27 g of methyldichlorophosphine in 30 ml of absolute ether was carefully added, and the mixture allowed to stand overnight. Then, after separating the precipitate, the solvent was distilled off and the residue distilled in an atmosphere of nitrogen. This yielded 23.85 g (56.5%) of the dithiol ester of methylphosphinous acid.

B.p. 83-85° (8 mm), n^{20}_D 1.5577, d_4^{20} 1.0378.

Found %: P 18.63, 18.70; S 38.45, 38.50. $C_5H_{13}S_2P$. Calculated %: P 18.40; S 38.11.

The dithioethyl ester of methyl phosphinous acid is a colorless, transparent liquid, easily soluble in alcohol, acetone, ether and other organic solvents but not soluble in water; it has an unpleasant odor.

2. The dithioethyl ester of methylphosphinic acid. By an analogous procedure 18 g (41.4%) of the dithioethyl ester of methylphosphinic acid was prepared from 11.5 g of metallic sodium in 150 ml of liquid ammonia and 30.5 g of diethyldisulfide with 33.25 g of the dichloride of methylphosphinic acid.

B.p. 135-138° (16 mm), n^{20}_D 1.5423, d_4^{20} 1.1412.

Found %: P. 16.56, 16.16; S 34.15, 34.22. $C_5H_{13}OS_2P$. Calculated %: P 16.80; S 34.80.

The dithioethyl ester of methylphosphinic acid is a colorless, transparent liquid with an unpleasant smell which is easily soluble in alcohol, ether, benzene and other organic solvents, but insoluble in water.

3. Oxidation of the dithioethyl ester of methylphosphinous acid. 5 g of the dithioethyl ester of methylphosphinous acid was placed in a flask equipped with a disperser, and nitrogen dioxide diluted with dry nitrogen was passed through at 20-30°. The end of the reaction is recognized by the appearance of a green color. Excess nitrogen oxide was removed with dry nitrogen. The substance was distilled in vacuo. The dithioethyl ester of methylphosphinous acid had a b.p. of 152-154° (25 mm), n^{20}_D 1.5418.

4. Transesterification of the dithioethyl ester of methylphosphinous acid (typical experiment). A mixture of 0.03 g-moles of the dithioethyl ester of methylphosphinous acid and 0.06 g-moles of alcohol was heated in the presence of metallic sodium at 160-180° for five hours. On conclusion of the heating, the reaction mixture was fractionated. The constants of the compounds are shown in Table 1.

5. Transesterification of the dithioethyl ester of methylphosphinic acid (typical experiment). A mixture of 0.03 g-moles of the dithioethyl ester of methylphosphinic acid and 0.09 g-moles of alcohol was heated in the presence of metallic sodium to form 170-200° (in the case of butyl alcohol, to form 130-160°) for five hours. Then the reaction mixture was fractionated. The constants of the compounds are shown in Table 2.

SUMMARY

It was shown that the alcoholysis of thiolphosphinites and thiolphosphonates yields esters of phosphinous and phosphinic acid.

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THE SYNTHESIS OF SOME ORGANOCHLOROSILANES

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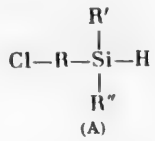
There is almost no information in the literature on tri-substituted silanes whose molecule contains an atom of silicon linked simultaneously to hydrogen and to a chlorinated organic radical (A). Meanwhile they are of interest for the purpose of preparing polymers with alternating atoms of silicon and carbon (for example the chain – Si – C_6H_4 – – Si –) by the thermal condensation of chlorine with hydrogen and silicon [1].

In the present study new compounds of this type – chloromethylmethylphenylsilane, chloromethyldiphenylsilane and chlorophenylmethylphenylsilane – were prepared by the reduction of the corresponding chlorosilanes by lithium aluminum hydride. It is known



(A)

that during this reduction a transfer of a hydride ion to the electron-poor center occurs; in this connection one might expect that reduction of chlorine at a more electropositive silicon atom would occur more easily and would not affect the chlorine and carbon atom. It is known, for example, that the reduction of chloromethyltrichlorosilane by lithium hydride (although it is less active than lithium aluminum hydride) yields only chloromethylsilane even in the presence of a three-fold excess of lithium hydride [2]. Even less probable is the occurrence of side reactions in reducing the chlorine at a carbon atom in chlorophenyl derivatives, since the reduction of chlorine in the phenyl radical occurs only with great difficulty. The reduction of chlorophenyldiphenylchlorosilane with a yield of chlorophenyldiphenylsilane of 56% has been mentioned in the literature [3].

In our experiments the reduction of chlorophenylmethylphenylchlorosilane was carried out.

$$4ClC_6H_4Si(CH_3)(C_6H_5)Cl + LiAlH_4 \longrightarrow 4ClC_6H_4Si(CH_3)(C_6H_5)H + AlCl_3 + LiCl$$

The reaction gave a yield of 69.5-72% of chlorophenylmethylphenylsilane regardless of the order in which the reagents were introduced.

The reduction of chloromethylmethylphenylchlorosilane was more complex

$$4ClCH_2Si(CH_3)(C_6H_5)Cl + LiAlH_4 \longrightarrow 4ClCH_2Si(CH_3)(C_6H_5)H + AlCl_3 + LiCl$$

When a solution of lithium aluminum chloride was poured into chlorosilane the yield of chloromethylmethylphenylsilane, amounted to 83% but there was practically no reduction of the chlorine in the chloromethyl group (apparently only traces of dimethylsilane were formed). When the order of mixing the reagents was reversed, the yield of chloromethylmethylphenylsilane amounted to only 56%, while the yield of dimethylphenylsilane increased sharply (9% of pure material was obtained).

The greatest difficulties were encountered in reducing chloromethyldiphenylchlorosilane.

$$4ClCH_2Si(C_6H_5)_2Cl + LiAlH_4 \longrightarrow 4ClCH_2Si(C_6H_5)_2H + LiCl + AlCl_3$$

Under optimum conditions the yield of chloromethyldiphenylsilane amounts to 67%; in this case the chlorine atom in the chloromethyl group is also reduced and methyldiphenylsilane is formed with a yield of 7%. Apparently

the rate of reduction of the chlorine at the silicon atom in chloromethyldiphenylchlorosilane is reduced because of the steric effect of the phenyl groups and becomes commensurate with the rate of reduction of chlorine in the chloromethyl group.

EXPERIMENTAL

1. Preparation of chloromethylmethylphenylchlorosilane. This product was prepared from 408 g of chloromethylmethyldichlorosilane and phenylmagnesium bromide obtained from 60 g of magnesium and 392.5 g of bromobenzene in 650 ml of ether. Distillation of the reaction mixture yielded 241.5 g (47%) of chloromethylmethylphenylchlorosilane, b.p. 116-124° (16 mm), n^{20}_D 1.5365 and 55.5 g (11%) of chloromethylmethylphenylchlorosilane, b.p. 125-135° (16 mm), n^{20}_D 1.5502, which apparently contained a considerable admixture of diphenyl. Chloromethylmethylphenylchlorosilane was obtained on redistillation.

B.p. 106-108° (8 mm), n^{20}_D 1.5340, d_4^{20} 1.1825, MR_D 53.93. $C_8H_{10}SiF_3$. Calculated 54.56.

The literature shows [4]: b.p. 136° (24 mm).

Found %: C 48.3, 48.3; H 5.3, 5.2; Cl 30.2, 31.7; Cl (hydrolyzed) 17.26, 17.05; Si 14.4, 14.2.* $C_8H_{10}Cl_2Si$. Calculated %: C 46.84; H 4.91; Cl 34.55; Cl (hydrolyzed) 17.28; Si 13.68.

2. Preparation of chloromethyldiphenylchlorosilane. This product was synthesized from 186 g of chloromethyltrichlorosilane and phenyl magnesium bromide obtained from 52.8 g of magnesium and 345.5 g of bromobenzene in 600 ml of ether. Distillation of the reaction mixture gave 84.5 g (31.3%) of chloromethyldiphenylchlorosilane.

B.p. 187-192° (10 mm), n^{20}_D 1.5935, d_4^{20} 1.2514.**

Found %: C 58.5, 58.3; H 4.5, 4.8; Cl 26.4, 26.8; Si 10.6, 10.9; Cl (hydrolyzed) 14.23, 14.19. $C_{13}H_{12}Cl_2Si$. Calculated %: C 58.43; H 4.53; Cl 26.54; Si 10.51; Cl (hydrolyzed) 13.27.

58.2 g (25.5%) of chloromethylphenyldichlorosilane was also separated from the reaction mixture.

B.p. 110-118° (12 mm), n^{20}_D 1.5422, d_4^{20} 1.2451.***

Found %: Cl (hydrolyzed) 32.55, 32.73. $C_7H_7Cl_3Si$. Calculated %: Cl (hydrolyzed) 31.43.

3. Preparation of chlorophenylmethylphenylchlorosilane. Chlorophenylmethylphenylchlorosilane was obtained from 564 g of chlorophenylmethyldichlorosilane**** and phenylmagnesium bromide, prepared from 60 g of magnesium and 392.5 g of bromobenzene in 600 ml of ether. On distillation, 339 g (48%) of chlorophenylmethylphenylchlorosilane with a b.p. of 165-175° (8 mm) was obtained. On redistillation, two fractions were obtained.

First: b.p. 168-172°(9 mm), 45.5 g, n^{20}_D 1.5795, d_4^{20} 1.1938, MR_D 74.42; calc. 74.40. Found %: Cl (hydrolyzed) 15.17, 15.16.

Second: b.p. 173-174° (9 mm), 280.2 g, n^{20}_D 1.5838, d_4^{20} 1.2078, MR_D 74.03.*****

Found %: C 57.9; H 4.54; Cl 27.0; Si 10.5; Cl (hydrolyzed) 13.47. $C_{13}H_{12}Cl_2Si$. Calculated %: C 58.43; H 4.53; Cl 26.54; Si 10.51; Cl (hydrolyzed) 13.27.

4. Reduction of chlorosilanes by lithium aluminum hydride. A) Chlorosilane was placed in a three-necked flask equipped with a stirrer, reflux condenser and a dropping funnel with a calcium chloride drying tube, 100 ml of ether was poured in and an ether solution of lithium aluminum hydride was added through the dropping funnel, with continuous stirring, at such a rate that the mixture boiled evenly. After all the solution had been added, the mix-

* The analytical data give evidence of an admixture of diphenyl in the substance. Inasmuch as the purification of chloromethylmethylphenylchlorosilane from an admixture of diphenyl is difficult while the chloromethylmethylphenylsilane obtained on reduction may be easily separated from diphenyl, we did not undertake the task of carefully purifying the chloromethylmethylphenylchlorosilane.

** Data on the constants of chloromethyldiphenylchlorosilane are not available in the literature.

*** The substance contains an admixture of diphenyl.

**** The substance was obtained by the catalytic dehydrocondensation of chlorobenzene with methyldichlorosilane and is a mixture of ortho-, meta- and para-isomers with d_4^{20} 1.2872 [5].

***** The isomers of chlorophenylmethylphenylchlorosilane are not described in the literature.

ture was boiled for six hours, then cooled in ice water and decomposed by the careful addition of previously chilled 5% hydrochloric acid. The ether layer was separated and the aqueous layer extracted three times with ether. The combined ether solutions were washed with water and dried over anhydrous magnesium sulfate. The ether was distilled off, and the remaining material distilled in vacuo.

B) Chlorosilane was dropped into an ether solution of lithium aluminum hydride at such a rate that the liquid boiled evenly. Then the mixture was boiled for from 2-6 hours. Decomposition of the reaction mixture and separation of the silane hydride was carried out in the same manner as in method A.

5. Preparation of chloromethylmethylphenylsilane. Experiment 1. A solution of lithium aluminum hydride was prepared from 6.4 g of lithium hydride and 53.4 g of aluminum bromide in 600 ml of ether. Reduction of 102.5 g of chloromethylmethylphenylchlorosilane was carried out as in method A. On distillation of the reaction products 2.3 g of a fraction boiling up to 97° (14 mm), n^{20}_D 1.5258, which was apparently a mixture of dimethylphenylsilane and chloromethylmethylphenylsilane, and also 70.5 g (83%) of chloromethylmethylphenylsilane, b.p. 97-105° (14 mm), n^{20}_D 1.5322 were obtained. After a second distillation the chloromethylmethylphenylsilane had the following constants.

B.p. 99-100° (14 mm), n^{20}_D 1.5326, d_4^{20} 1.0485, MR_D 50.49; calc. 50.69.

Found %: C 56.10, 56.90; H 6.59, 6.60; Cl 20.80, 20.66; Si 16.50, 16.10. $C_8H_{11}ClSi$. Calculated %: C 56.30; H 6.49; Cl 20.77; Si 16.44.*

Experiment 2. A solution of lithium aluminum hydride was prepared from aluminum bromide obtained from 6 g of aluminum and 17 ml of bromine in 250 ml of ether, and 7.2 g of lithium hydride. Reduction of 102.5 g of chloromethylmethylphenylchlorosilane was carried out according to method B. The reaction mixture was boiled for six hours. The following were obtained by distillation:

a) 5.9 g (9.0%) of dimethylphenylsilane.

B.p. 55-70° (21 mm), n^{20}_D 1.4992, d_4^{20} 0.8842, MR_D 45.23. $C_8H_{12}SiF_3$. Calculated 45.75. From the literature [6]: b.p. 57° (20 mm), n^{20}_D 1.4988, d_4^{20} 0.876.

b) 12.9 g of a fraction with b.p. 71-105° (21 mm), n^{20}_D 1.5265 which was apparently a mixture of dimethylphenylsilane and chloromethylmethylphenylsilane.

c) 47.8 g (56%) of chloromethylmethylphenylsilane with b.p. 106-115° (21 mm), n^{20}_D 1.5322.

6. Preparation of chloromethyldiphenylsilane. A solution of lithium aluminum hydride was prepared from 3.2 g of lithium hydride and 26.7 g of aluminum bromide in 300 ml of ether. Reduction of 66.6 g of chloromethyldiphenylchlorosilane was carried out in accordance with method A. Distillation yielded the following products: a) 6.5 g of a fraction with b.p. 86-179° (17 mm) which was apparently a mixture of methyldiphenylsilane and chloromethyldiphenylsilane; b) 39 g (67%) of chloromethyldiphenylsilane with b.p. 180-190° (17 mm), n^{20}_D 1.5868.

After redistillation the chloromethyldiphenylsilane had the following constants.

B.p. 175-180° (15 mm), n^{20}_D 1.5842, d_4^{20} 1.1089, MR_D 70.25. $C_{13}H_{13}ClSiF_6$. Calculated 70.46.

Found %: C 66.70; H 5.70; Cl 15.50, 15.61; Si 11.57. $C_{13}H_{13}ClSi$. Calculated %: C 67.10; H 5.63; Cl 15.24; Si 12.06.**

Repeated distillation of the fraction with a b.p. of 86-179° (17 mm) yielded 3.5 g (7%) of methyldiphenylsilane.

B.p. 150-160 (17 mm), n^{20}_D 1.5762, d_4^{20} 0.9975, MR_D 65.91. $C_{13}H_{14}SiF_6$. Calculated 65.62.

Data from the literature [7]: b.p. 70-90° (0.1 mm), 82° (0.15 mm), n^{20}_D 1.5747, d_4^{20} 0.9973.

7. Preparation of chlorophenylmethylphenylsilane. A solution of lithium aluminum hydride was prepared from 6 g of aluminum, 17 ml of bromine and 7.2 g of lithium hydride in 550 ml of ether. 152 g of chlorophenyl-

* Chloromethylmethylphenylsilane is not described in the literature.

** Chloromethyldiphenylsilane is not described in the literature.

methylphenylchlorosilane was reduced in accordance with method A. On distillation of the reaction products, 7.8 g of a fraction with a b.p. of up to 172° (25 mm) and 92.2 g (69.5%) of chlorophenylmethylphenylsilane was obtained.

B.p. 172-180° (25 mm), n^{20}_D 1.5795, d_4^{20} 1.0982, MR_D 70.50. $C_{13}H_{13}ClSiF_6$. Calculated 70.46.

Found %: C 67.3, 67.4; H 5.7, 5.46; Cl 15.1, 15.9; Si 12.06; H_{sl} 0.40. $C_{13}H_{13}ClSi$. Calculated %: C 67.10; H 5.63; Cl 15.24; Si 12.06; H_{sl} 0.43.*

By reducing chlorophenylmethylphenylchlorosilane according to method B, using identical quantities, 96 g (72%) of chlorophenylmethylphenylsilane with a b.p. of 156-160° (10 mm) was obtained.

SUMMARY

1. A method of reducing chloroorganochlorosilanes was worked out.

2. Chloromethylmethylphenylsilane, chloromethyldiphenylsilane and chlorophenylmethylphenylsilane, not previously described in the literature, were prepared and identified.

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* Chlorophenylmethylphenylsilane is not described in the literature.

REACTIONS OF HALOMETALALCOHOLATES

X. A NEW METHOD OF SYNTHESIZING MONOHYDROXYTRIARYLMETHANES

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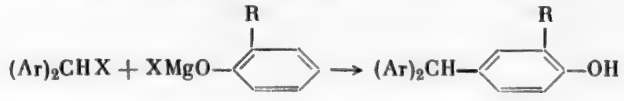
In a previous paper [1] a method of synthesizing monohydroxytriarylmethane was described which was based on the action of the esters of formic or oxalic acids on a mixture consisting of halomagnesiumdiarylcarbinolate and phenolate (or naphtholate). The carbinolate is converted into a diarylmethylhalide [2] by the action of the ester. This then reacts with halomagnesiumphenolates (naphtholates) which remain unchanged under these conditions, to form monohydroxytriarylmethane.

$$(Ar)_2CHOMgX + HCOOC_2H_5 \longrightarrow (Ar)_2CHX$$



The present investigation was undertaken for the purpose of further studying this reaction.

The following regularities of the reaction described were determined on the basis of a comparatively large amount of experimental material.

1. Phenolates with an unsubstituted para position form para isomers of monohydroxytriarylmethanes; those which are substituted form ortho isomers. Since the formation of monohydroxytriarylmethanes is connected with the reversal of the phenol radical, the substituents remain in their previous position in relation to the hydroxyl group.

2. The formation of monohydroxytriarylmethanes proceeds normally not only in the absence of, but also in the presence of diarylcarbinolate ortho substituents. The formation of monohydroxytriarylmethanes fails to occur only in the case where there are two ortho substituents in each of the two aryl radicals, since the halomagnesium-carbinolates of such carbinols are converted into diarylmethanes under the influence of the esters of formic or oxalic acid [2]. However when two ortho substituents are present in one aryl radical, ethers are formed.

3. Phenolates that have substituents in the meta position, under the reaction conditions assumed, form ethers of the type of aryldiarylmethyl ether or a mixture of substances consisting of ethers and monohydroxytriarylmethanes. The basic reason for such a course of the reaction is undoubtedly a steric factor. On reversal of the m-phenol radical, the substituent is in the ortho position to the diarylmethyl radical. If ortho substituents are lacking in the latter, then, as indicated, monohydroxytriarylmethanes are formed in addition to aryldiarylmethyl ethers; in the presence of ortho substituents, however, only ethers are formed. If substituents are located simultaneously in the meta and ortho positions, the reaction gives monohydroxytriarylmethanes with a hydroxy group in the para position.

4. Neither monohydroxytriarylmethanes nor aryldiarylmethyl ethers are formed when two ortho substituents are present in the phenolate. In this case the reaction stops at the stage where diarylmethyl halide is formed.

In the preparation of monohydroxytriarylmethanes it is not essential to start with carbinols that have been synthesized in advance. It is very convenient to combine this reaction with the preparation of the carbinol itself by means of organo-magnesium synthesis. It is only necessary to have an excess of Grignard reagent so that there is sufficient for the subsequent conversion of the phenol into halomagnesium phenolate.

EXPERIMENTAL

1. Synthesis of 2,2',5"-trimethyl-2"-hydroxytriphenylmethane. Di-o-tolylcarbinol and p-cresol (0.066 g-moles each) were dissolved in a triple volume of absolute diethyl ether, and to this was added an ether solution (three

volumes) of ethylmagnesium bromide (0.132 g-moles). The ethyl ester of formic acid (0.066 g-moles) was added to the ether solution of bromomagnesium-o-tolylcarbinolate and p-cresolate, after which the reaction mixture was heated for three hours, decomposed with water and 10% acetic acid, the ether layer separated and washed with a 10% solution of sodium bicarbonate and water. After drying the ether solution by means of calcined sodium sulfate, the solvent was distilled off and the product purified by recrystallization from petroleum ether (fraction 70-80°). Yield 65%. M.p. 156°.

Found %: C 87.20; H 7.23; OH 5.4. $C_{22}H_{22}O$. Calculated %: C 87.37; H 7.34; OH 5.6.

The synthesis of a designated hydroxytriarylmethane may be combined with the preparation of the corresponding carbinol by organomagnesium synthesis.

An ether solution of ethylformate (0.066 g-moles) was added to an ether solution of o-tolylmagnesium bromide (0.2 moles). The mixture was heated for one hour, after which p-cresol (0.066 g-moles), dissolved in the same solvent, was added. One more portion of ethyl formate (0.066 g-moles) was added to the solution of bromomagnesium-o-tolylcarbinolate and p-cresolate and the mixture heated for three hours. Further treatment was the same as in the preceding experiment. The yield was 60%. As proof of the structure of the compound 2,2'-5"-trimethyl-2"-ethoxytriphenylcarbinol was obtained from di-o-tolylketone and 5-methyl-ethoxyphenylmagnesium bromide. The only difference from the ordinary conditions of organomagnesium synthesis was the fact that, in order to increase the temperature of the reaction, the ether, after the reagents had been mixed, was replaced by toluene. The toluene solution was heated on a boiling water bath for three hours. After hydrolysis, the volatile products were driven off with steam. M.p. 115° (from petroleum ether).

Found %: C 83.01; H 7.46; OH 4.5; OC_2H_5 12.5. $C_{24}H_{26}O_2$. Calculated %: C 83.20; H 7.57; OH 4.9; OC_2H_5 13.0.

The carbinol synthesized was reduced to 2,2',5"-trimethyl-2"-ethoxytriphenylmethane. This was done by dissolving the substance in a six-fold quantity of 98% acetic acid and boiling it with a 1.5 fold quantity of zinc dust. M.p. 100° (from petroleum ether).

Found %: C 87.05; H 7.90; OC_2H_5 13.2. $C_{24}H_{26}O$. Calculated %: C 87.23; H 7.93; OC_2H_5 13.6.

On heating this compound, dissolved in 98% acetic acid, with hydrobromic acid (d 1.48) for four hours, 2,2',5"-trimethyl-2"-hydroxytriphenylmethane was obtained. M.p. 156°. A mixed melting point test with the product synthesized by the method under study showed no depression.

2. Synthesis of 2-methyl-5-isopropyl-4-hydroxytriphenylmethane. As in the preceding experiment, an ether solution of ethylmagnesium bromide (0.132 g-moles) and then diethyl oxalate (0.066 g-moles) was added to a mixture of the original substances (benzhydrol and thymol) (0.066 g-moles each) dissolved in absolute ether. The mixture was heated for three hours. After hydrolysis the product was separated by distillation and purified by recrystallization from petroleum ether. B.p. 220-222° (5 mm), m.p. 137°. Yield 68%.

Found %: C 87.12; H 7.58; OH 5.1. $C_{23}H_{24}O$. Calculated %: C 87.30; H 7.65; OH 5.4.

This compound was also synthesized by two other methods. In the first method benzaldehyde (0.066 g-moles) was first added to an ether solution of phenyl magnesium bromide (0.132 g-moles), then thymol (0.066 g-moles) and finally diethyloxalate (0.066 g-moles) also dissolved in ether. The yield was 70%. In the second method 0.066 g moles each of ethyl formate, thymol and ethyl formate again were added successively to phenylmagnesium bromide (0.2 g-moles). The yield was 72%.

The structure of the monohydroxytriphenylmethane formed was established as follows. By reacting 2-methyl-5-isopropyl-4-methoxyphenylmagnesium bromide with benzophenone under the usual conditions of the organo-magnesium synthesis, 2-methyl-5-isopropyl-4-methoxytriphenylcarbinol was obtained. Yield 70%. M.p. 110° (from petroleum ether).

Found %: C 83.05; H 7.46; OH 4.6; OCH_3 8.5. $C_{24}H_{26}O_2$. Calculated %: C 83.20; H 7.57; OH 4.9; OCH_3 8.9.

By heating in glacial acetic acid with zinc dust, the carbinol was reduced to 2-methyl-5-isopropyl-4-methoxytriphenylmethane. M.p. 89° (from methyl alcohol).

Found %: C 87.04; H 7.83; OCH_3 9.0. $C_{24}H_{26}O$. Calculated %: C 87.23; H 7.93; OCH_3 9.4.

By heating this compound, dissolved in acetic acid, with hydrobromic acid, 2-methyl-5-isopropyl-4-hydroxytriphenylmethane was obtained. M.p. 137°. A mixed melting point test with the compound prepared by the method under investigation showed no depression.

3. Synthesis of 2,2'-dimethyl-4"-hydroxytriphenylmethane. The order of mixing the original materials was as follows: o-tolylmagnesium bromide (0.2 g-moles), ethyl formate (0.066 g-moles ; heated for one hour), phenol (0.066 g-moles), ethyl formate (0.066 g-moles ; heated for three hours). Yield 65%. M.p. 136° (from petroleum ether).

Found %: C 87.29; H 6.87; OH 5.7. $C_{21}H_{20}O$. Calculated %: C 87.46; H 6.99; OH 5.9.

The same method was used to establish the structure of the 2,2'-dimethyl-4"-hydroxytriphenylmethane. 2,2'-Dimethyl-4"-ethoxytriphenylcarbinol was synthesized from di-o-tolylketone and 4-ethoxyphenylmagnesium bromide (heated for three hours; the ether was replaced by toluene and after hydrolysis the volatile products were distilled off with steam). Yield 69%. M.p. 125° (from petroleum ether).

Found %: C 82.95; H 7.19; OH 4.9; OC_2H_5 12.8. $C_{23}H_{24}O_2$. Calculated %: C 83.10; H 7.28; OH 5.1; OC_2H_5 13.5.

Under the conditions mentioned above, the carbinol was reduced to 2,2'-dimethyl-4"-ethoxytriphenylmethane. M.p. 99° (from petroleum ether).

Found %: C 87.14; H 7.53; OC_2H_5 14.8. $C_{23}H_{24}O$. Calculated %: C 87.30; H 7.64; OC_2H_5 14.2.

By cleaving by means of hydrobromic acid, the latter compound was converted into 2,2'-dimethyl-4"-hydroxytriphenylmethane. M.p. 136°. A mixed melting point test showed no depression.

4. Synthesis of 2,2',3"-trimethyl-4"-hydroxytriphenylmethane. The order of mixing the original materials was the same as in the preceding experiment, but o-cresol was used instead of phenol. The yield was 70%. M.p. 114° (from petroleum ether).

Found %: C 87.52; H 7.37; OH 5.5. $C_{22}H_{22}O$. Calculated %: C 87.38; H 7.34; OH 5.6.

The structure of the product synthesized was demonstrated in the same way by first forming 2,2',3"-trimethyl-4"-ethoxytriphenylcarbinol, then 2,2',3"-trimethyl-4"-ethoxytriphenylmethane, and finally 2,2',3"-trimethyl-4"-hydroxytriphenylmethane. The intermediate products were not purified to an analytically pure state.

5. Synthesis of 2-methyl-4-hydroxytriphenylmethane and m-tolylbenzhydryl ether. From bromomagnesium-benzhydrolate and m-cresolate in the presence of diethyloxalate two products were obtained which were separated by distillation and purified by recrystallization from petroleum ether. The first product, which did not contain a hydroxyl group, was m-tolylbenzhydryl ether and was obtained in 52% yield. M.p. 124°; the literature [3] gives 125°.

Found %: C 87.32; H 6.59. $C_{20}H_{18}O$. Calculated %: C 87.55; H 6.62.

The yield of the second product – 2-methyl-4-hydroxytriphenylmethane – was 33%. M.p. 142°.

Found %: C 87.35; H 6.51; OH 6.0. $C_{20}H_{18}O$. Calculated %: C 87.55; H 6.62; OH 6.2.

In order to establish the structure of this compound, 2-methyl-4-ethoxyphenylmagnesium bromide was allowed to react with benzophenone which gave 2-methyl-4-ethoxytriphenylcarbinol. M.p. 91° (from petroleum ether). Yield 55%.

Found %: C 82.75; H 6.88; OH 5.3; OC_2H_5 13.8. $C_{22}H_{22}O_2$. Calculated %: C 82.98; H 6.97; OH 5.4; OC_2H_5 14.2.

On reducing it with zinc dust, 2-methyl-4-ethoxytriphenylmethane was obtained. M.p. 73° (from petroleum ether).

Found %: C 87.22; H 7.30; OC_2H_5 14.5. $C_{22}H_{22}O$. Calculated %: C 87.37; H 7.34; OC_2H_5 14.9.

Cleavage of the latter by means of hydrobromic acid gave 2-methyl-4-hydroxytriphenylmethane. M.p. 142°. A mixed melting point test with a sample synthesized directly showed no depression.

6. Synthesis of 2-methyl-4'-hydroxytriphenylmethane. The starting materials were (0.066 g-moles each): phenyl-o-tolylcarbinol, phenol (converted by the action of ethylmagnesium bromide to bromomagnesiumcarbinolate and phenolate) and ethyl formate. Heating was continued for three hours. Yield 66%. M.p. 101° (from petroleum ether).

Found %: C 87.57; H 6.50; OH 6.0. $C_{20}H_{18}O$. Calculated %: C 87.55; H 6.62; OH 6.2.

The structure was demonstrated in the same manner as in the preceding experiments. Because the intermediate products were only available in small quantities, they were not brought to the analytical level of purity. Only the end product was purified and analyzed. It had the same properties as the compound prepared by the method under investigation.

7. Synthesis of 2,2'-dimethyl-5-isopropyl-4-hydroxytriphenylmethane. This compound was prepared by two methods. In the first method the sequential order of mixing the original materials dissolved in ether was: o-tolylmagnesium bromide (0.2 g-moles), benzaldehyde (0.1 g-mole; heating for one hour), thymol (0.1 g-mole) and ethyl formate (0.1 g-mole; heating for three hours).

In the second method the order of mixing was: phenyl-o-tolylcarbinol, thymol (0.1 g-mole each), ethylmagnesium bromide (0.2 g-moles) and diethyloxalate (0.1 g-mole). Subsequent treatment of the reaction mixture has been described above. The yield in both the first and second methods was 65%. M.p. 127°.

Found %: C 87.05; H 7.82; OH 4.9. $C_{24}H_{26}O$. Calculated %: C 87.23; H 7.93; OH 5.1.

The structure of the compound obtained was established by synthesizing 2,2'-dimethyl-5-isopropyl-4-methoxytriphenylcarbinol from phenyl-o-tolylketone and 2-methyl-5-isopropyl-4-methoxyphenylmagnesium bromide and subsequently converting it into 2,2'-dimethyl-5-isopropyl-4-hydroxytriphenylmethane. Only the final product was purified and analyzed.

8. Synthesis of m-tolyl-di-o-tolylmethyl ether. Ethyl formate (0.066 g-mole) was added to an ether solution of o-tolylmagnesium bromide (0.2 g-mole) and heated for one hour; then 0.066 g-mole of m-cresol and more ethyl formate (0.066 g-mole) were added and heated for three hours. After hydrolysis the volatile products were distilled off with steam. The hydroxyl group was not detected in the final product. M.p. 206° (from petroleum ether). Yield 70%.

Found %: C 87.22; H 7.30. M 304.8. $C_{22}H_{22}O$. Calculated %: C 87.37; H 7.34. M 302.4.

In order to establish the structure of the ether of di-o-tolylbromomethane (m.p. 66-67°), it was mixed with m-cresol in the presence of KOH [4]. A mixed melting point with the reaction product showed no depression.

9. Synthesis of (phenyl-o-tolylmethyl)-m-tolyl ether. The ether was obtained by the action of ethyl formate on a mixture of bromomagnesiumphenyl-o-tolylcarbinolate and m-cresolate. Volatile products were distilled off with steam. No hydroxyl group was detected in the product. M.p. 144° (from petroleum ether). Yield 75%.

Found %: C 87.28; H 6.91. $C_{21}H_{20}O$. Calculated %: C 87.46; H 6.99.

10. Synthesis of (2,4,6-trimethylbenzhydryl)-phenyl ether. A mixture consisting of bromomagnesiumphenylmesitylcarbinolate, phenolate and ethyl formate in equimolecular proportions was heated for four hours. No hydroxyl group was detected in the resulting product. Yield 45%. M.p. 139° (from alcohol).

Found %: C 87.19; H 7.23. $C_{22}H_{22}O$. Calculated %: C 87.37; H 7.34.

SUMMARY

1. Study was continued on a new method of synthesizing monohydroxytriarylmethanes, based on the action of esters of formic or oxalic acid on a mixture consisting of halomagnesiumdiarylcarbinolate and phenolate.

2. The basic laws for the course of this reaction, depending on the structure of the starting materials, were worked out.

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ISOMERIZATION OF POLYMETHYLENE HYDROCARBONS BY MEANS OF ALUMINUM CHLORIDE

XXV. THE ISOMERIZATION OF CYCLOPENTYLCYCLOHEPTANE

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In our previous studies we investigated the behavior of uncondensed bicyclic hydrocarbons containing a five-membered ring in the presence of aluminum chloride, in particular dicyclopentyl [1], dicyclopentylmethane [2] and cyclopentylcyclohexane [3].

Further study of this reaction appears opportune to us in view of the fact that it has recently become essential to explain the behavior of various types of hydrocarbons, and bicyclic ones in particular, which, in view of their constants may enter the kerosene fraction of petroleum. Reactions with aluminum chloride are widely used in the treatment of petroleum.

In the present investigation we studied the behavior of cyclopentycycloheptane in the presence of aluminum chloride.

By analogy with the results we obtained previously on the isomerization of bicyclic hydrocarbons [1-3], one might assume that cyclopentylcycloheptane would isomerize to a decahydronaphthalene (dimethyldecalin) system under the influence of aluminum chloride. In view of the fact that data on the physical constants of many isomers of dimethyldecalin are lacking in the literature, in order to establish the structure of the reaction products we used, in addition to spectral analysis, the method of dehydrogenation catalysis. The use of the method of dehydrogenation catalysis in this case is expedient because, as in known from the work of Khromov and Balenkova [4], cyclopentylcycloheptane on dehydrogenation over platinized carbon forms a mixture of the following hydrocarbons: 1-methyl-1-cyclopentylcyclohexane, isomers of 1-methyl-1-amylcyclohexane, phenylcyclopentane, isomers of tolylcyclopentane and methylamylbenzene. Consequently, in the process of dehydrogenation, the cyclopentane ring which is part of the cyclopentylcycloheptane system, partially undergoes hydrogenolysis and the seven-membered ring isomerizes to methylcyclohexane and is then dehydrogenated. In the aromatic part of the catalytic products, the authors detected no dimethylnaphthalenes.

If our assumptions had proved correct, dimethyldecalins – products of the isomerization of cyclopentylcycloheptane – should have been converted into dimethylnaphthalenes by dehydrogenation catalysis.

During the course of the study it was found that when the reagents react at 0°, cyclopentylcycloheptane does not undergo any changes. When the temperature of the reaction was about 35°, the cyclopentylcycloheptane constants changed noticeably and approached the constants of dimethyldecalins [5]. It was impossible to interpret the spectra of the isomerization products of cyclopentylcycloheptane precisely, since data on the spectra of isomeric dimethyldecalins are lacking in the literature. However the study did show that lines characteristic of the original hydrocarbons were absent from the spectrum of the reaction product, and that intense new lines had appeared.

On dehydrogenation of the reaction product, the product of catalysis had a sharp odor of naphthalene. It consisted of a very small quantity of a liquid product, n^{20}_D 1.5906, which was not further studied because the quantity was insufficient, and of a crystalline product with a m.p. of 69-70°, from which a picrate melting at 113° was obtained. The melting point of the crystalline fraction of the reaction product corresponds with the melting points of solid dimethylnaphthalenes (from 63 to 110°) that are given in the literature [6]. The slight divergence of the melting point of 113° for the picrate we obtained from the melting points of the picrates of dimethylnaphthalenes given in the literature (from 123 to 148°) [6, 7] may be explained, apparently, by the fact that, on isomerization, cyclopentylcycloheptane forms a mixture of isomeric dimethylnaphthalenes.

Analysis showed that the crystalline hydrocarbon we obtained corresponded to a compound with an empirical formula of $C_{12}H_{12}$ (dimethylnaphthalene).

Thus, on carrying out dehydrogenation catalysis, a sharp difference in behavior between the original cyclopentylcycloheptane in this reaction and its isomerization products was observed. On the basis of the data obtained it may be considered as proved that cyclopentylcycloheptane forms a decalin system which is more stable in the presence of aluminum chloride.

From the data of the study it follows, moreover, that five and seven-membered rings in the cyclopentylcycloheptane molecule behave the same as the corresponding monocyclanes in the presence of aluminum chloride; specifically, the five-membered ring is enlarged and the seven-membered ring is reduced to a six-membered ring.

EXPERIMENTAL

The cyclopentylcycloheptane needed for the study was synthesized by the method of Khromov and Balenkova [4] by starting from cyclohexanone which is converted to cycloheptanone by the action of diazomethane. The condensation product of cycloheptanone and cyclopentadiene was reduced by hydrogen in the presence of nickel to cyclopentylcycloheptane.

The cyclopentylcycloheptane was chromatographed twice on silica-gel and distilled in vacuo at 7 mm in a column with an effectiveness of 80 theoretical plates, after which it was again chromatographed.

B.p. 238-240° (747 mm), 101° (7 mm); freezing point −84.76 ± 0.01°, n^{20}_D 1.4812, d_4^{20} 0.8911, MR_D 53.11. $C_{12}H_{22}$. Calculated 53.21.

The purity of the cyclopentylcycloheptane was 99.230 ± 0.076%.

The literature gives [4]; b.p. 93-93.5° (8 mm), n^{20}_D 1.4812, d_4^{20} 0.8912, MR_D 53.11.

The combination dispersion spectrum of the cyclopentylcycloheptane prepared by us coincided essentially with the spectrum of this hydrocarbon as given in the literature [4]: 224 (0); 246 (0); 265 (0); 335 (0); 387 (1); 735 (4); 769 (0); 846 (0); 897 (5); 948 (1.5, db);* 1007 (4, db); 1032 (2, db); 1085 (6); 1133 (1); 1277 (5, broad); 1347 (1); 1442 (10).

Experiment 1. Aluminum chloride was added to the hydrocarbon which had been cooled to 0°. After 15 hours the hydrocarbon was separated from the aluminum chloride, washed with acid, water, a solution of alkali, again with water, dried over calcium chloride and distilled over metallic sodium. The constants of the reaction product (b.p. 235-293° at 758 mm, n^{20}_D 1.4808, d_4^{20} 0.8906) coincided almost perfectly with the constants of the original cyclopentylcycloheptane. The spectrum of the reaction product did not differ from that of the original cyclopentylcycloheptane.

Experiment 2. On adding aluminum chloride to the hydrocarbon, the temperature began to rise slowly to 35°, and then gradually declined to the original value (16°). After similar purification, the reaction product was distilled.

B.p. 222-226° (734 mm), n^{20}_D 1.4722, d_4^{20} 0.8713, MR_D 53.37; calc. 53.21.

Found %: C 86.83, 86.60; H 13.26, 13.46. $C_{12}H_{22}$. Calculated %: C 86.70; H 13.30.

Spectrum of the isomerization product: 224 (0); 246 (0); 272 (0.5); 284 (0); 318 (0); 343 (0); 364 (0); 387 (0); 455 (0); 499 (0.8);*755 (4); 769 (0.8); 787 (1); 846 (3.5); 1032 (2.5); 1044 (6); 1133 (0); 1160 (5); 1196 (5); 1237 (1.5); 1267 (2); 1347 (3); 1354 (2); 1442 (10); 1456 (2, db).

Dehydrogenation of the reaction product. As a preliminary the original cyclopentylcycloheptane was passed over platinized carbon containing 5% of platinum at 300-320°. The catalyzed product had n^{20}_D 1.5046 after the first passage. The literature shows [4] that after the first passage of cyclopentylcycloheptane, the product of catalysis had n^{20}_D 1.4981, after the second 1.5030; after the third 1.5059.

Then the product of the reaction, which after the first passage had become crystalline, was again passed over the same catalyst under the same conditions. After a second recrystallization from alcohol, the product of the re-

* The underlined numbers are lines that are characteristic of cyclopentylcycloheptane.

reaction melted at 69-70°, and this temperature did not change on further recrystallization. A picrate with m.p. 113° was obtained from this product.

Found %: C 92.24, 92.30; H 7.74, 7.82. $C_{12}H_{22}$. Calculated %: C 92.31; H 7.69.

SUMMARY

1. The isomerization of cyclopentylcycloheptane under the influence of aluminum chloride was studied.

2. The action of aluminum chloride on cyclopentylcycloheptane (at 16-35°) leads to an expansion of the five-membered ring and a reduction of the seven-membered in the cyclopentylcycloheptane system to six-membered rings with the formation of dimethyldecalin.

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SYNTHESIS AND SOME REACTIONS OF 1-PHENYL-1-HYDROXY-2-METHOXYMETHYLCYCLOHEXANE

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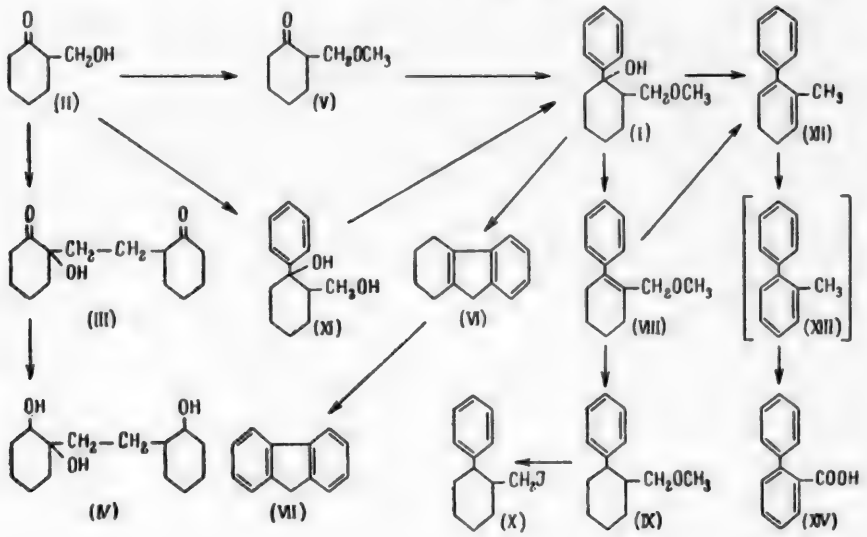
The present paper is devoted to a more detailed examination of the method of converting 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane (I) to the corresponding desoxy compounds.

The starting material for the synthesis of (I) was 2-hydroxymethylcyclohexane (II) which was prepared by the condensation of cyclohexanone and formaldehyde [1, 2]. A study of the chemical properties of (II) showed that this compound is stable only in the narrow pH range from 6 to 7. On increasing the pH, polymerization of (II) occurs with vigorous evolution of heat and the formation of a mixture of polymers which were not studied in detail. On reducing the pH, (II) is easily converted into (II) which was previously described in the literature [3] as 2-[β-cyclohexanone-2'-yl)-ethyl]-2-hydroxycyclohexanone-1. We have shown that the formation of (III) proceeds in the presence of traces of hydrochloric acid, or upon the addition of catalytic quantities of iodine. The hydroxy group in (III) is apparently located in an axial position and is strongly shielded. In this connection (III) does not form derivatives at the hydroxy group on treatment with phenylisocyanate, on benzoylation and on acetylation in the presence of p-toluenesulfoacid. At the same time the hydroxy group in (III) may be detected by the method of Chugaev-Tserevitinov, and on reduction by means of sodium borohydride, (III) is quantitatively converted into triol (IV).



The high lability of (II), when acted upon by both acid and alkaline reagents, required the selection of very gentle conditions in order to prepare 2-methoxymethylcyclohexanone (V). Preliminary experiments showed that on converting (II) to the sodium derivative with subsequent treatment with methyl iodide, only polymeric products are formed. 2-Methoxymethylcyclohexanone (V) was obtained in 70% yield by treating (II) with methyl iodide and silver oxide in boiling ether.

When (V) was allowed to react with phenyllithium and with phenylmagnesium bromide, 1-phenyl-hydroxy-2-methoxymethylcyclohexane (I) was obtained with yields of 40.6 and 62% respectively. It should be noted that in both

cases only one of the two possible diastereoisomers of (I) was obtained. This is in agreement with the data in the literature according to which, in the reaction of 2-hydroxymethylcyclohexanone with phenylmagnesium bromide, only one diasteroisomer of 1-phenyl-1-hydroxymethylcyclohexane (XI) is formed [2].

In order to determine the correlation between (XI) and the corresponding methoxyderivative of (I), 1-phenyl-1-hydroxy-2-hydroxymethylcyclohexane (XI), prepared by the reaction of 2-hydroxymethylcyclohexanone with phenylmagnesium bromide [2], was converted into the sodium alcoholate, which, on treatment with methyl iodide, gave (I).

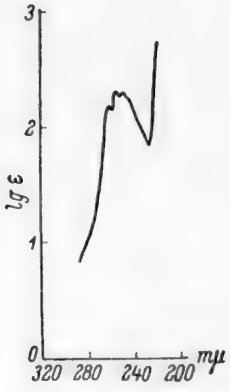
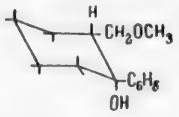


Fig. 1. UV spectrum of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane (I).

All three samples of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane (I), prepared by different methods (from 2-methoxymethylcyclohexane and phenylmagnesium bromide; from 2-methoxymethylcyclohexane and phenyl lithium; and from 1-phenyl-1-hydroxy-2-hydroxymethylcyclohexane) were identical in physical constants and in their infrared and UV spectra (Figs. 1 and 2). In all three cases only one diastereoisomer of (I) was formed. In view of the fact that an equatorial position of the methoxymethyl group in the 2-methoxymethylcyclohexanone (V) used in the synthesis of (I) is most probable and that for nucleophilic linking an equatorial entrance of the phenyl nucleus must take place, the most probable structure of (I) is 1e-phenyl-1a-hydroxy-2e-methoxymethylcyclohexane.



Such a structure of (I) would allow us to assume that this compound would be easily dehydrated (transelimination). As a matter of fact, preliminary experiments showed that even when (I) reacts with concentrated hydrochloric acid at 0°, partial dehydration takes place.

As a result of a study of various methods of dehydrating (I) it was shown that, depending on the character of the dehydrating agent and the reaction conditions, various compounds are formed. When potassium bisulfate is used at 150° (I) is converted into 1-phenyl-2-methoxymethyl-3,4,5,6-tetrahydrobenzene (VIII) with a yield of 70%. The

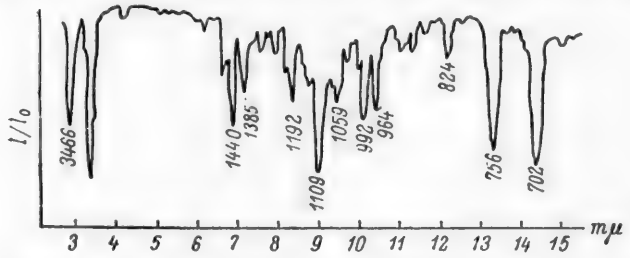


Fig. 2. Infrared spectrum of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane (I).

use of phosphorus pentoxide in boiling xylene as a dehydrating agent leads not only to dehydration, but also to the further cleavage of a molecule of methyl alcohol with the simultaneous closing of the cyclopentane ring and the formation of 1,2,3,4-tetrahydrofluorene (VI). This conversion opens up a new method of synthesizing derivatives of 1,2,3,4-tetrahydrofluorene which, up to the present, have been prepared by the cyclodehydration of 2-benzylidencyclohexanone by aluminum chloride [4]. The yield of (VI) according to the method described in the literature is 40%, while on treating (I) with phosphorus pentoxide it is 47%. The identity of the two compounds was shown by a comparison of their constants and UV spectra, and also by the conversion of (VI) to fluorene (VII) by dehydrogenation with platinum. The UV spectrum of (VII) prepared in this way is identical with the UV spectrum of fluorene as described in the literature [5], and a mixed melting point test shows no depression.

A study of the dehydration of (I) by heating in an anhydrous solvent with the addition of catalytic quantities of iodine and the simultaneous azeotropic distillation of water showed that the use of benzene and o-xylene as the

boiling solvent gives various reaction products. When the process is carried out in boiling benzene,(VIII) is formed with a yield of 69%. When the reaction is carried out in boiling o-xylene, dehydration is accompanied by the cleavage of a molecule of methyl alcohol with the formation of a compound which does not contain oxygen. The same compound is formed on heating (I) with anhydrous oxalic acid for one hour at 170-190°. The hydrocarbon obtained in both cases has the same elementary composition as tetrahydrofluorene; however, it is not 1,2,3,4-tetrahydrofluorene and does not yield fluorene on dehydrogenation. A comparison of the infrared spectra of this hydrocarbon and 1,2,3,4-tetrahydrofluorene showed that along with the common absorption bands (1473 cm^{-1}) which are characteristic of the phenyl nucleus, the new hydrocarbon has an absorption band at 1375 cm^{-1} which is characteristic of the CH_3 group, and an absorption band at 1595 cm^{-1} which is characteristic of a system with conjugated double bonds. Both these absorption bands are absent in the infrared spectrum of 1,2,3,4-tetrahydrofluorene. The spectral data permit us to assume that this hydrocarbon is 1-phenyl-2-methyl-4,5-dihydrobenzene (XII). The correctness of this assumption was confirmed by purely chemical means. Hydrocarbon (XII), on dehydrogenation in the presence of sulfur, was converted into 2-methylbiphenyl, which, without further purification, was oxidized to biphenyl-2-carboxylic acid (XIV) by means of potassium permanganate.

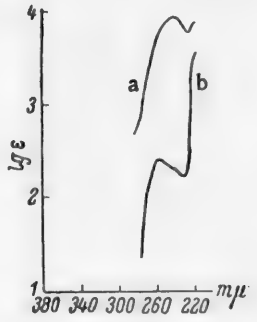


Fig. 3. Ultraviolet spectra. 1) 1-Phenyl-2-methoxymethyl-3,4,5,6-tetrahydrobenzene (VIII); b) 1-phenyl-2-methoxymethylcyclohexane (IX).

It should be noted that the conversion of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane (I) to (XII) may be accomplished step-by-step. 1-Phenyl-2-methoxymethyl-3-4,5,6-tetrahydrobenzene (VIII), formed by heating (I) with iodine at 80° (in boiling benzene), may be separated from the reaction mixture and converted into (XII) by heating with iodine in boiling o-xylene.

Reduction of the double bond in 1-phenyl-2-methoxymethyl-3,4,5,6-tetrahydrobenzene (VIII) was accomplished in the presence of a nickel catalyst under a pressure of 110 atm. and a temperature of 220° for five hours. The yield of 1-phenyl-2-methoxymethylcyclohexane (IX) in this case amounted to 89%. At a lower pressure (50 atm.) the double bond in (VIII) is not hydrogenated in the presence of a platinum catalyst prepared according to Adams.

The structure of 1-phenyl-2-methoxymethylcyclohexane was confirmed by UV spectroscopy (Fig. 3). In the UV spectrum of (IX) there is an absorption band at 256 mμ with an intensity of log ε 2.4 which indicates the absence of a double bond linked with the phenyl nucleus. In the original compound (VIII) where, apparently, such a linking of the phenyl radical by a double bond exists, the absorption band has a higher intensity (log ε 3.94).

On heating 1-phenyl-2-methoxymethylcyclohexane (IX) in boiling hydriodic acid in the presence of red phosphorus, it is converted into 1-phenyl-2-iodomethylcyclohexane (X) with a yield of about 80%.

EXPERIMENTAL

2-[β-(Cyclohexanone-2'-yl)-ethyl]-2-hydroxycyclohexanone-1 (III). 1) Two drops of concentrated hydrochloric acid were added to 32.8 g of 2-hydroxymethylcyclohexanone. The reaction mixture was warmed and from the uniform solution that was formed, which had a pH of 2, colorless crystals of (III) began to separate out. The reaction mixture was heated for three hours on a boiling water bath. The crystals that formed were filtered off. The yield of (III) was 21.2 g (67%). Colorless crystals, m.p. 154-155° (from heptane) [3]. The compound was soluble in alcohols, chloroform, acetone, ether and benzene, was slightly soluble in heptane and in petroleum ether and insoluble in water.

Found %: C 70.25; H 9.45; OH 7.32, 7.02. $C_{14}H_{22}O_3$. Calculated %: C 70.56; H 9.29; OH 7.15.

2) 0.02 g of crystalline iodine was added to 6.4 g of 2-hydroxymethylcyclohexanone and the reaction mixture allowed to stand for 30 days at room temperature. The material crystallized completely. The reaction mixture was stirred with two ml of petroleum ether and filtered. 3.9 g of (III) (65.5%) was obtained. A mixed melting point test with sample (III) prepared according to method 1 showed 154-155°.

Bisphenylhydrazone, m.p. 191-193 (from xylene) [3].

Found %: C 74.50; H 8.14; N 13.24. $C_{26}H_{34}ON_4$. Calculated %: C 74.60; H 8.18; N 13.39.

Dioxime, m.p. 191-193° (from aqueous alcohol) [3].

Found %: N 10.38. $C_{14}H_{24}O_3N_2$. Calculated %: N 10.44.

2-[β-(Cyclohexanol-2'-yl)-ethyl]-2-hydroxycyclohexanol-1 (IV). 2.38 g of 2-[β-(cyclohexanone-2'-yl)-ethyl]-2-hydroxycyclohexanone-1 was dissolved in 120 ml of methanol. 6 g of sodium borohydride was added to the solution in portions during the course of 30 minutes. The reaction mixture was stirred for two hours at room temperature, after which the methanol was distilled off in vacuo. 40 ml of water was added to the residue and extracted with ether; the ether solution was dried over potash. The ether was distilled off and the remaining material distilled in vacuo. 2.35 g of (IV) (98%) was obtained. On standing the material crystallized. Colorless crystals, m.p. 153.5-154.5° (from acetone) [3]. The substance is easily soluble in alcohols, chloroform, and dioxane, not very soluble in ethyl acetate, acetone and benzene; and insoluble in water and petroleum ether.

Found %: C 69.28, 69.04; H 10.80, 10.50. $C_{14}H_{26}O_3$. Calculated %: C 69.36; H 10.82.

2-Methoxymethylcyclohexanone (V). 10.4 g of silver oxide was added to a solution of 3.84 g of 2-hydroxymethylcyclohexanone in 30 ml of anhydrous ether. The resulting suspension was stirred with 12.8 g of methyl iodide. Stirring was continued for 12 hours at room temperature and then for five hours more at the boiling point. The precipitate was filtered off and washed with ether. The ether filtrate was evaporated in vacuo and the remaining material distilled. B.p. 77-78° (5 mm), n^{25}_D 1.4520. 3 g (70.5%) of (V) was obtained.

It was a colorless, oily substance, easily soluble in the usual organic solvents, but insoluble in water.

Found %: C 67.44; H 10.15; OCH_3 21.61. $C_8H_{14}O_2$. Calculated %: C 67.57; H 9.93; OCH_3 21.82.

1-Phenyl-1-hydroxy-2-methoxymethylcyclohexane (I). 1) 18 g of 2-methoxymethylcyclohexanone in 25 ml of anhydrous ether was added, during the course of 30 minutes with stirring and cooling by means of ice water, to phenylmagnesium bromide which had been prepared from 78.5 g of bromobenzene and 12.2 g of magnesium in 100 ml of anhydrous ether. After stirring at room temperature for two hours, the reaction mixture was poured over ice and treated with 85 ml of 18% hydrochloric acid. The acid solution was extracted with ether. The ether extract was dried over potash, and after removing the solvent, the remaining material was distilled in vacuo. B.p. 124-125° (3 mm), n^{25}_D 1.5251. The yield of (I) was 17 g (62%).

It was a colorless, oily liquid and was easily soluble in the usual organic solvents, but insoluble in water. For the UV spectrum see Fig. 1; for the infrared spectrum see Fig. 2.

Found %: C 76.46, 76.58; H 9.25, 9.00. $C_{14}H_{20}O_2$. Calculated %: C 76.31; H 9.13.

2) A solution of 13.1 g of 2-methoxymethylcyclohexanone in 50 ml of anhydrous ether was added, during the course of an hour while stirring and cooling with ice water, to 420 ml of an ether solution of phenyl lithium that contained 31 g of phenyl lithium as determined by titration. The reaction mixture was stirred in an atmosphere of nitrogen for two hours at room temperature, after which it was poured over 800 g of ice. The ether solution was separated, the aqueous layer extracted with ether, and the combined ether extracts dried over calcined potash. The ether was distilled off and the remaining material distilled in vacuo. B.p. 124-125° (3 mm). The yield of (I) was 9.8 g (40.6%). Its properties, constants, infrared and UV spectra were identical with those of (I) as prepared in experiment 1.

Found %: C 76.50, 76.20; H 9.22, 8.91; OCH_3 13.86. $C_{14}H_{20}O_2$. Calculated %: C 76.31; H 9.13; OCH_3 14.10.

3) 2 g of 1-phenyl-1-hydroxy-2-hydroxymethylcyclohexane, prepared by the reaction of 2-hydroxymethylcyclohexanone with phenylmagnesium bromide [2], was dissolved in an anhydrous mixture of 35 ml of xylene and 15 ml of ether. 0.23 g of metallic sodium was added to this solution, and the mixture stirred and heated at 80° for four hours. The metallic sodium gradually reacted, and a white, flocculent precipitate of the alcoholate separated out. Then 10 g of methyl iodide was added to the reaction mixture and stirring was continued at 80° for a further four hours. During this period the precipitate of alcoholate gradually went into solution, and a heavier precipitate of sodium iodide separated out. 15 ml of water was added to the reaction mixture. The aqueous solution was extracted with ether. The combined ether-xylene solutions were dried over calcined calcium chloride. The solvents were distilled off. The remaining material was distilled in vacuo. B.p. 124-125° (3 mm). 1.5 g (68%) of (I) was obtained which was identical in properties, constants, infrared and UV spectra with the (I) obtained in experiments 1 and 2.

Found %: OCH_3 14.04. $C_{14}H_{20}O_2$. Calculated %: OCH_3 14.10.

Dehydration of 1-phenyl-1-hydroxyl-1-hydroxy-2-methoxymethylcyclohexane by means of phosphorus pentoxide. A mixture of 10.1 g of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane, 30 g of phosphorus pentoxide

and 100 ml of xylene was boiled, with stirring, for four hours. The xylene solution was decanted. 20 ml of ice water was added to the precipitate and extracted with xylene. The combined xylene extracts were dried over calcium chloride and distilled in vacuo. B.p. 132-136 (6 mm). Yield 3.7 g (47.5%).

The substance, which was 1,2,3,4-tetrahydrofluorene (VI), formed colorless crystals, m.p. 56-57° (from alcohol [4]). It was easily soluble in ether, benzene, acetone and chloroform, only slightly soluble in alcohol and insoluble in water.

UV spectrum: λ_{max} (log ε) 260 mμ (4.09), 300 mμ (2.44), 319 mμ (1.42) [4].

Found %: C 91.87; H 8.27. $C_{13}H_{14}$. Calculated %: C 91.77; H 8.23.

Dehydrogenation of 1,2,3,4-tetrahydrofluorene (VI). 0.38 g of (VI) and 0.1 g of platinum black were heated in a current of nitrogen at 260° for 30 minutes. After cooling the reaction mixture, 4 ml of boiling alcohol was added. The platinum black was filtered off. 0.05 g of colorless crystals of fluorene (VII), m.p. 113-114° [6] separated out from the alcohol solution on cooling. The substance showed no depression of the melting point when mixed with fluorene, and it was identical to fluorene in its UV spectrum [5].

Dehydration of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane by means of iodine. a) 1-Phenyl-2-methoxymethyl-3,4,5,6-tetrahydrobenzene (VIII). 8.8 g of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane and 0.2 g of iodine were heated in 50 ml of boiling benzene in a Dean-Stark apparatus, with simultaneous azeotropic distillation of the water formed. After 2.5 hours, when 0.6 ml of water had been driven off, heating was discontinued. In order to remove the iodine, the benzene solution was extracted twice with a saturated aqueous solution of sodium bisulfite, washed with water and dried over calcium chloride. The benzene was distilled off in vacuo. The remaining material was distilled and a fraction with a b.p. of 117-118° (4 mm), n^{25}_D 1.5465 was collected. The yield of (VIII) was 5.6 g (69%).

This was a colorless, oily substance which was easily soluble in the ordinary organic solvents, but insoluble in water. For the UV spectrum, see Fig. 3.

Found %: C 83.16; H 8.59. $C_{14}H_{18}O$. Calculated %: C 83.12; H 8.96.

b) 1-Phenyl-2-methyl-4,5-dihydrobenzene (XII). 1) 5.5 g of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane and 0.2 g of iodine were heated in a Dean-Stark apparatus in 50 ml of boiling o-xylene with simultaneous azeotropic distillation of the water formed. After three hours the xylene was distilled off in vacuo. The remaining material was distilled. B.p. 91-92° (3.5 mm), n^{25}_D 1.5468. The yield of (XII) was 2.85 g (61.6%).

It was a colorless, oily substance, easily soluble in the usual organic solvents and fairly insoluble in water.

Infrared spectrum (in cm^{-1}): 1471 (C_6H_5), 1375 (CH_3), 1595 (C = C − C = C).

Found %: C 91.65; H 8.11. $C_{13}H_{14}$. Calculated %: C 91.77; H 8.23.

2) 5.5 g of 1-phenyl-2-methoxymethyl-3,4,5,6-tetrahydrobenzene and 0.4 g of iodine were heated in 40 ml of boiling o-xylene in a Dean-Stark apparatus for 2.5 hours. The xylene was distilled off. The remaining material was distilled in vacuo and the fraction collected which boiled at 91-92° (3.5 mm), n^{25}_D 1.5648. The yield of (XII) was 1.4 g (30.3%).

Biphenyl-2-carboxylic acid (XIV). A mixture of 4 g of 1-phenyl-2-methyl-4,5-dihydrobenzene and 0.75 g of sulfur was heated for four hours at 235-240° and a residual pressure of 200 mm. Formation of hydrogen sulfide began at 180°. After completion of the dehydrogenation, the reaction mixture was distilled in vacuo. The fraction containing 2-methylbiphenyl (XII) (2.45 g) boiling at 95-97° (3 mm) was collected and without further purification was mixed with a solution of 6.1 g of potassium permanganate in 400 ml of water. This was boiled and stirred for 18 hours. Manganese dioxide was filtered off and the filtrate extracted with ether in order to remove unoxidized (XIII). The aqueous solution was acidified with hydrochloric acid and biphenyl-2-carboxylic acid (XIV) was extracted with ether. The yield of (XIV) was 1.74 g (37.4% based on XII or 60% based on XIII), b.p. 110 (from benzene) [7].

Found %: C 78.83, 79.05; H 5.16, 5.10. $C_{13}H_{10}O_2$. Calculated %: C 78.78; H 5.05.

Dehydration of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane by means of potassiumbisulfate (1-phenyl-2-methoxymethyl-3,4,5,6-tetrahydrobenzene) (VIII). A mixture of 6.6 g of 1-phenyl-1-hydroxy-2-methoxymethyl-

cyclohexane and 3.3 g of anhydrous potassium bisulfate pulverized to a fine powder was heated to 150° for 30 minutes and then for a further 30 minutes at 150° with a residual pressure of 35-45 mm. Then the residual pressure was reduced to 3.5 mm and the reaction mixture distilled. 3 g of anhydrous potassium bisulfate pulverized to powder was added to the distillate. The reaction mixture was again heated for 30 minutes to 150°, and then for a further 30 minutes at 150° and a residual pressure of 35-45 mm. The residual pressure was reduced to 4 mm and the reaction mixture distilled. The fraction (VIII) boiling at 117-118° (4 mm), n^{25}_D 1.5465 was collected. The yield was 4.2 g (70%).

The substance was identical with (VIII) prepared by the dehydration of (I) by means of iodine in boiling benzene.

1-Phenyl-2-methoxymethylcyclohexane (IX). 3.5 g of 1-phenyl-2-methoxymethyl-3,4,5,6-tetrahydrobenzene (VIII) in 70 ml of alcohol was hydrogenated with 1 g of a nickel catalyst in an autoclave under a hydrogen pressure of 110 atm. at 220°. The hydrogenation reaction was continued for five hours. The catalyst was filtered off and the alcohol solution evaporated in vacuo. 1-Phenyl-2-methoxymethylcyclohexane (IX) was distilled. B.p. 107-108° (4 mm), n^{25}_D 1.5203. The yield of (IX) was 3.15 g (89%).

This was a colorless, oily liquid. It was easily soluble in the usual organic solvents, but insoluble in water.

UV spectrum (Fig. 3): λ_{max} 256 mμ (log ε 2.4).

Found %: C 82.08; H 9.83. $C_{14}H_{20}O$. Calculated %: C 82.25; H 9.85.

1-Phenyl-2-iodomethylcyclohexane (X). A mixture of 1 g of 1-phenyl-2-methoxymethylcyclohexane, 0.8 g of red phosphorus and 50 ml of hydroiodic acid (d 1.83) was boiled for one hour. After the reaction mixture had cooled, 50 ml of ether was added, the red phosphorus residue was filtered off and the aqueous layer was extracted with ether. The combined ether extracts were washed with a 10% aqueous solution of sodium bisulfite in order to remove iodine, the ether was distilled off and the remaining material distilled in vacuo. B.p. 137-138° (4 mm), n^{25}_D 1.5808. The yield of (X) was 1.17 g (79.5%).

This was an oily substance which was easily soluble in the usual organic solvents, but insoluble in water.

Found %: I 42.03, 42.13; C 52.86; H 5.85. $C_{13}H_{17}I$. Calculated %: I 42.33; C 52.00; H 5.66.

SUMMARY

1. The synthesis of 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane from 2-hydroxymethylcyclohexanone was accomplished: a) through 2-methoxymethylcyclohexanone by the use of phenylmagnesium bromide; b) through 2-methoxymethylcyclohexanone by the use of phenyl lithium; c) through 1-phenyl-1-hydroxy-2-hydroxymethylcyclohexane. In each case only one diastereoisomeric product was obtained, for which the formula 1e-phenyl-1a-hydroxy-2e-methoxymethylcyclohexane was proposed on the basis of conformational analysis.

2. It was shown that when 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane is dehydrated by means of phosphorus pentoxide, 1,2,3,4-tetrahydrofluorene is formed; when it is dehydrated by boiling with iodine in o-xylene and oxalic acid 1-phenyl-2-methyl-4,5-dihydrobenzene is formed; when it is dehydrated with sodium bisulfate in boiling benzene 1-phenyl-2-methoxymethyl-3,4,5,6-tetrahydrobenzene is formed.

3. A method of converting 1-phenyl-1-hydroxy-2-methoxymethylcyclohexane into the corresponding desoxy derivative in two steps, with a yield of 61%, was worked out.

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SOME PROPERTIES OF ENOL ACETATES

VIII. THE BROMINATION OF ENOL ACETATES OF CYCLOPENTANONE AND CYCLOHEPTANONE BY MEANS OF N-BROMOSUCCINIMIDE

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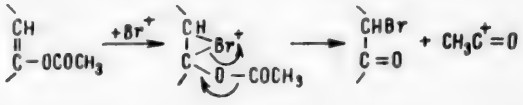
The reaction of enol acetates of carbinol compounds with N-bromosuccinimide has received little attention. Efforts to introduce bromine into the allyl position of enol acetates of ketosteroids have not been successful; products of dehydrobromination – α, β-unsaturated ketones – have been obtained [1, 2].

In previous studies we have shown that in a number of cases bromo-substituted enol acetates have been formed by the reaction of the enol acetates of carbinol compounds with N-bromosuccinimide. In the case of the enol acetates of the aldehydes and methyl ketones of the aliphatic series, β-bromo-substituted enol acetates are obtained [3, 4], while in the case of the enol acetates of cyclobutanone and cyclohexanone α-bromo-substituted enol acetates are obtained [5, 6].

In the present study, the reaction of enol acetates of cyclopentanone and cycloheptanone with N-bromosuccinimide has been investigated. In this case the corresponding α-bromoketones are formed, namely, α-bromocyclopentanone with a yield of 66% and α-bromocycloheptanone (70.7%).* Thus in both cases a cleavage of the acetyl residue with regeneration of the carbonyl group occurs along with the introduction of bromine.**

The different behavior of the enol acetates of cyclobutanone and cyclohexanone in the reaction studied by us, on the one hand, and of cyclopentanone and also cycloheptanone on the other hand, is in agreement with the difference, previously mentioned in the literature, between the behavior of some other derivatives of cyclobutane and cyclohexane and analogous derivatives of cyclopentane and cycloheptane [9, 20, 21]. The unusual behavior of the enol acetates mentioned above in the reaction with N-bromosuccinimide is due, apparently, to steric peculiarities of these cyclic systems. One might suppose that bromination in these cases, which leads to the formation of different products, takes place by a different mechanism. The bromination of the enol acetates of cyclobutanone and cyclohexanone proceeds by a radical mechanism which is usual for the N-bromosuccinimide reaction. However the reaction of the enol acetates of cyclopentanone and cycloheptanone with N-bromosuccinimide probably proceeds by an ionic mechanism,*** for which one may postulate the intermediate formation of a bromo-ionic complex.



The formation of α-bromoketones in the reaction studied may also be explained by the fact that the spatial structure of the enol acetates of cyclopentanone and cycloheptanone is favorable to the formation of a cyclic transitional state in accordance with the following.

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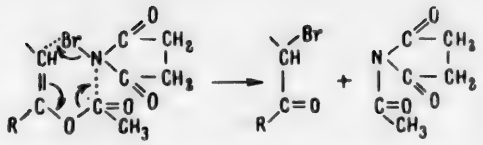
* It is interesting to note that the enol acetate of 2,3-benzocycloheptanone-1 on reacting with N-bromosuccinimide gives 2,3-benzocycloheptene-6-one-1 [7].

** An analogous result, i.e., the regeneration of the carbonyl group during halogenation, was observed previously in the action of N-iodosuccinimide on the enol acetates of ketosteroids [8].

*** A number of cases have previously been mentioned in the literature where bromination by means of N-bromosuccinimide appears to be an ionic reaction [10, 11].



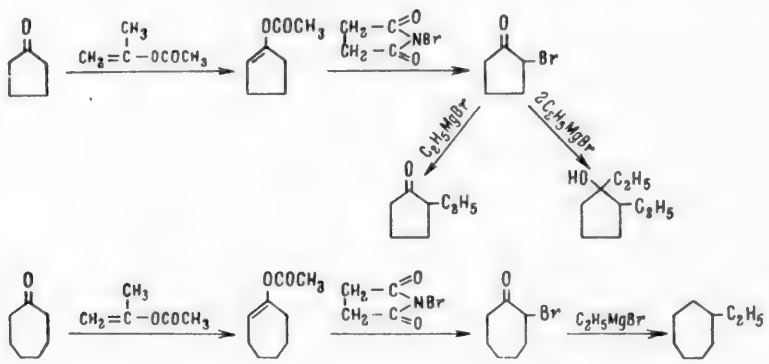
Preservation of the enol acetate group on bromination of the enol acetates of cyclobutanone and cyclohexanone and its decomposition under these conditions into the enol acetates of cyclopentanone and cycloheptanone is analogous to the fact, previously mentioned in the literature [12], that the semiketals of cyclobutanone and cyclohexanone are considerably more stable in chemical reactions than the semiketals of cyclopentanone and cycloheptanone.

The method which we worked out for the preparation of α-bromocyclopentanone and α-bromocycloheptanone is more convenient than the previously known methods for preparing these α-bromoketones. On brominating cyclopentanone and cycloheptanone by means of bromine in the presence of $CaCO_3$ [13], and also by the action of bromine in chloroform solution [14, 15], the yields of α-bromoketones are lower, because of the formation of a considerable quantity of dibromides, than in the method described in this paper (calculating in the latter case on the original ketone, i.e., for two steps). On brominating cyclopentanone by means of dioxane dibromide, the principal product of the reaction is a dibromoketone [16]. In our method only monobromoketones with a strictly determined position of the halogen are formed. We also consider that the preparation of α-bromoketones by the bromination of enol acetates by means of N-bromosuccinimide is simpler than the method previously proposed (similar to the preparation of α-bromocyclohexanone) for the synthesis of α-bromoketones by first combining bromine with the double bond of the enol acetates [17].

The reaction of the α-bromoketones which we prepared with alkylmagnesium halides was studied. When α-bromocyclopentanone reacts with one mole of ethylmagnesium bromide in ether, α-ethylcyclopentanone is obtained (yield 9%), while when the ratio of reagents is 1 : 2, 1,2-diethylcyclopentanol-1 is obtained (10.1%). The reaction of α-bromocycloheptanone with ethylmagnesium bromide (1 : 1) gives α-ethylcycloheptanone with a yield of 25.8%. The formation of α-alkylketones by the reaction of alkylmagnesium bromides with bromoketones confirms the fact that the bromine atom in the latter is located in the α-position to the carbonyl group.

We succeeded in preparing the original enol acetates of cyclopentanone and cycloheptanone, which were first synthesized by Mannich [18] in poor yield, with yields of 80.25% and 68.9% respectively by reacting the ketones with isopropenyl acetate in the presence of a catalyst – acetylsulfoacetic acid. The reaction proceeds on warming with slow distillation of the acetone formed.* The structure of the enol acetates, obtained by elementary and functional analysis, and also by means of the infrared spectra which have the following characteristic intense frequencies: in the spectrum of the enol acetate of cyclopentanone – 1766 (C = O), 1031 and 1215 (the = C – O – C group), 2975 (= C – H) and 1680 cm^{-1} (C = C); in the spectrum of the enol acetate of cycloheptanone – 1760 (C = O), 1028 and 1239 (= C – O – C), 2930 (= C – H) and 1695 cm^{-1} (C = C).

All the reactions described in the present paper may be represented by the following scheme.



* As we showed previously, when acetic anhydride reacts with cyclopentanone in the presence of sulfuric acid, it is not possible to obtain the enol acetate – the diacetate of the hydrated form of the ketone is obtained [19].

EXPERIMENTAL

1. Preparation of the enol acetate of cyclopentanone. A mixture of 180 g of cyclopentanone, 428.6 g of isopropenyl acetate [6], 5.5 g of acetylsulfoacetic acid and 0.4 g of copper acetate was heated in flask for 7.5 hours, with slow distillation of acetone, through a column; during this period isopropenyl acetate, in a quantity equivalent to the acetone driven off, was added each hour. Upon completion of the reaction the mixture was cooled, stirred with a solution of 12.5 g of sodium bicarbonate and 125 ml of water, the organic layer separated, and the aqueous layer repeatedly extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether distilled off. 216.5 g (80.25%) of the enol acetate of cyclopentanone was obtained by fractionation in vacuo.

B.p. 42-42.7° (8 mm) [18], n^{20}_D 1.4451, d_4^{20} 1.0071, MR_D 33.32; calc. 33.51.

Found %: C 67.07, 66.90; H 8.18, 8.13. Saponification coefficient 446.7. Bromine number 128.9. $C_7H_{10}O_2$. Calculated %: C 66.64; H 7.99. Saponification coefficient 443.9. Bromine number 126.7.

Infrared spectrum: 829, 942, 1031, 1069, 1178, 1215, 1260, 1310, 1351, 1383, 1446, 1680, 1766, 1845, 2869, 2975 cm^{-1}.

2. Preparation of the enol acetate of cycloheptanone. The reaction was carried out in the same way as for the enol acetate of cyclopentanone. Initial quantities: 15 g of cycloheptanone, 26.75 g of isopropenyl acetate, 2 g of acetylsulfoacetic acid and 0.2 g of copper acetate. Distillation of acetone was carried on for five hours. The treatment was as above. On distillation in vacuo, 14.18 g (68.9%) of the enol acetate of cycloheptanone was obtained.

B.p. 74.1-74.8° (4 mm) [18], n^{20}_D 1.4621, d_4^{20} 0.9982, MR_D 42.49; calc. 42.87.

Found %: C 69.95, 69.91; H 9.26, 9.31. Saponification coefficient 364.2. Bromine number 107.0. $C_9H_{14}O_2$. Calculated %: C 70.09; H 9.15. Saponification coefficient 363.1. Bromine number 103.8.

Infrared spectrum: 843, 920, 967, 1028, 1075, 1095, 1125, 1157, 1239, 1378, 1455, 1695, 1760, 2853, 2930 cm^{-1}.

3. Bromination of the enol acetate of cyclopentanone by means of N-bromosuccinimide. A mixture of 15 g of the enol acetate of cyclopentanone, 21.2 g of N-bromosuccinimide (a molar ratio of 1 : 1), 10.5 ml of anhydrous CCl_4 and 10.5 ml of anhydrous $CHCl_3$ was heated on a water bath in a flask with a reflux condenser. When the temperature of the bath was 50°, a vigorous reaction began in the flask. After stopping the reaction all the N-bromosuccinimide went into solution. The cooled reaction mixture was filtered free from a small quantity of precipitate and the filtrate washed with water. The organic layer was dried by means of calcined calcium of α-bromocyclopentanone was obtained by fractionation in vacuo.

B.p. 79.8-80° (7 mm), n^{20}_D 1.5094, d_4^{20} 1.5730, MR_D 31.04; calc. 30.71 [14, 15, 22].

Found %: C 36.62; H 4.40; Br 48.75. C_5H_7OBr. Calculated %: C 36.84; H 4.33; Br 49.02.

4. Bromination of the enol acetate of cycloheptanone by means of N-bromosuccinimide. A mixture of 15 g of the enol acetate of cycloheptanone, 17.3 g of N-bromosuccinimide and 20 ml of carbon tetrachloride was heated on a water bath in a flask with a reflux condenser. A vigorous reaction began at a bath temperature of 80°. The treatment was as above. On distillation in vacuo, 13.23 g (70.7%) of α-bromocycloheptanone was obtained.

B.p. 99° (6 mm), n^{20}_D 1.5132, d_4^{20} 1.4278, MR_D 40.23; calc. 40.20 [22].

Found %: C 44.03, 43.83; H 5.73, 5.88. $C_7H_{11}OBr$. Calculated %: C 43.99; H 5.80.

5. Preparation of α-ethylcyclopentanone. The reaction was carried out in a three-necked flask equipped with a stirrer, a dropping funnel and a reflux condenser with a calcium chloride tube. The Grignard reagent was prepared from 4.07 g of Mg and 21.5 g of C_2H_5Br in 120 ml of absolute ether. A solution of 24 g of α-bromocyclopentanone in 240 ml of absolute ether was slowly added, with vigorous stirring and cooling with a mixture of snow and salt, to the cooled ether solution of Grignard reagent which had been diluted with 120 ml of absolute ether. After the material had been added, the mixture was stirred, with cooling, for 1.5 hours; then it was heated on a water bath at the boiling point of ether. The reflux condenser was replaced by a descending condenser and ~420 ml of ether was distilled off while stirring was continued. After cooling, a solution of NH_4Cl was added to the flask until the magnesium salts which had precipitated at first were dissolved. After repeated extraction with ether, the combined ether extracts were dried over calcined calcium chloride and the solvent was distilled off in vacuo. After repeated distillation in vacuo, 1.48 g (9%) of α-ethylcyclopentanone was obtained.*

* Replacement of ether by tetrahydrofuran or benzene, and also reversing the order of adding the reagents failed to increase the yield of α-ethylcyclopentanone.

B.p. 43-45° (7 mm), n^{20}_D 1.4438, d_4^{20} 0.9282, MR_D 32.16; calc. 32.29 [23, 24]. Ketone content 99.2% (by formation of oxime).

Found %: C 74.83, 74.91; H 11.01, 10.89. $C_7H_{12}O$. Calculated %: C 74.95; H 10.78.

Semicarbazone, m.p. 187.5-188° (from aqueous alcohol) [23, 24].

Found %: N 24.89, 24.96. $C_8H_{15}ON_3$. Calculated %: N 24.83.

6. Preparation of 1,2-diethylcyclopentanol-1. Grignard reagent was prepared from 6.78 g of Mg and 38.64 g of C_2H_5Br and 200 ml of absolute ether. A solution of 22.75 g of α-bromocyclopentanone in 120 ml of tetrahydrofuran was added to the chilled Grignard reagent drop by drop with vigorous stirring and cooling by means of ice; then the mixture was stirred for 30 minutes in the cold. The reflux condenser was replaced by a descending one and the ether distilled off with the simultaneous addition of 150 ml of tetrahydrofuran. After distilling off the ether (~160 ml) the mixture was heated at the boiling point for five hours under a reflux condenser. Treatment as above. A yield of 2.0 g (10.1%) of 1,2-diethylcyclopentanol-1 was obtained by fractionating in vacuo.

B.p. 80-82° (7 mm), n^{20}_D 1.4779 [25].

Found %: C 75.87, 75.91; H 12.86, 12.89; OH 12.11, 12.08. $C_9H_{18}O$. Calculated %: C 75.99; H 12.75; OH 11.96.

7. Preparation of α-ethylcycloheptanone. Grignard reagent was prepared from 1.53 g of Mg and 8.59 g of C_2H_5Br and 50 ml of absolute ether and added to a solution of 10 g of α-bromocyclopentanone in 75 ml of absolute ether. After the Grignard reagent had been added, the reaction mixture was heated for ten hours at the boiling point of ether. After the usual treatment, 1.89 g (25.8%) of α-ethylcycloheptanone was obtained.

B.p. 70-71° (7 mm) [26], n^{20}_D 1.4715, d_4^{20} 0.9415, MR_D 41.66; calc. 41.75. Ketone content 99.9% (by formation of oxime).

Found %: C 77.06, 77.12; H 11.61, 11.69. $C_9H_{16}O$. Calculated %: C 77.01; H 11.50.

Semicarbazone, m.p. 140-140.5° (from alcohol) [26].

Found %: N 21.41, 21.45. $C_{10}H_{19}ON_3$. Calculated %: N 21.30.

SUMMARY

1. It was found that when the enol acetates of cyclopentanone and cycloheptanone react with N-bromosuccinimide, α-bromoketones – α-bromocyclopentanone (yield 66%) and α-bromocycloheptanone 70.7% – are formed. The reaction may be used as a convenient method of preparing these compounds.

2. By reacting α-bromocyclopentanone with ethylmagnesium bromide, α-ethylcyclopentanone (at a molar ratio of 1 : 1) and 1,2-diethylcyclopentanol-1 (at a molar ratio of 1 : 2) are formed. α-Ethylcycloheptanone was synthesized by the reaction of α-bromocycloheptanone with ethylmagnesium bromide at a molar ratio of 1 : 1.

3. Methods of preparing the enol acetates of cyclopentanone (yield 80.25%) and cycloheptanone (68.9%) by the reaction of the corresponding ketones with isopropenyl acetate in the presence of acetylsulfoacetic acid were worked out.

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BICYCLIC SYSTEMS DERIVED FROM 2,6-LUTIDINE

V. DIQUATERNARY SALTS OF α,ω-BIS[9-METHYL-3,9-DIAZABICYCLO-(3,3,1)-NONANO-3]-ALKANES

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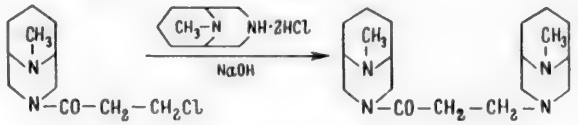
In a previous paper [1] we described the synthesis of a series of 3-substituted 9-methyl-3,9-diazabicyclo-(3,3,1)-nonanes and also diquaternary salts of α,ω-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-alkanes containing hydrocarbon chains of 4, 5 and 6 methylene groups. These compounds showed pharmacological activity, especially the diquaternary salts of 1,4-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-butane which have definite curare-like properties. In this connection it appeared interesting to us to continue the synthesis of this series of compounds and to prepare diquaternary salts containing hydrocarbon chains of 3 and 2 methylene groups.

Three variations in procedure were used to prepare the quaternary salts of 1,3-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-propane.

I. Malonyl-bis{3-[9-methyl-3,9-diazabicyclo-(3,3,1)-nonane]} was prepared by the reaction of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane with the dichloride of malonic acid in a manner analogous to the synthesis of diquaternary salts described in a previous paper [2]. However, efforts to reduce this diamide to the corresponding amine by means of lithium aluminum hydride did not give the desired results. A mixture of products was obtained from which it was impossible to separate individual compounds.

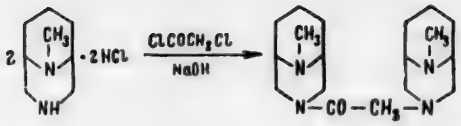
II. 9-Methyl-3,9-diazabicyclo-(3,3,1)-nonane was acetylated in position 3. The acetyl derivative was converted into a quaternary salt with methyl iodide and then was saponified with dilute hydrobromic acid which resulted in the formation of the iodohydrate of 9-methyl-9-methyliodide-3,9-diazabicyclo-(3,3,1)-nonane. By heating this compound with the theoretical quantity of caustic soda in methyl alcohol, 9-methyl-9-methyliodide-3,9-diazabicyclo-(3,3,1)-nonane was formed. However the reaction of this compound with 1,3-diiodopropane for the purpose of preparing the quaternary salt we were seeking did not succeed. The original substance was recovered in all cases.

III. The diquaternary salts of 1,3-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-propane were prepared, starting from the previously described 3-(β-chloropropionyl)-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane [1] by reacting the latter with the dichlorohydrate of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane in anhydrous alcohol in the presence of three moles of caustic soda.



The 3-{β-[9'-methyl-3',9'-diazabicyclo-(3',3',1')-nonano-3']-propionyl}-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane thus obtained was reduced, by means of lithium aluminum hydride, to 1,3-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-propane, from which the diquaternary salts were prepared with methyl iodide and dimethyl sulfate.

1,2-Bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-ethane was prepared by reacting the dichlorohydrate of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane with the chloride of monochloracetic acid in a solution of water and alkali.



The 3-{β-[9'-methyl-3',9'-diazabicyclo-(3',3',1')-nonano-3']-acetyl}-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane was reduced without preliminary distillation (since this causes it to decompose completely), and the reduced product was converted into the diquaternary salt.

EXPERIMENTAL

Malonyl-bis{3-[9-methyl-3,9-diazabicyclo-(3,3,1)-nonane]}. 5 g of the dichlorohydrate of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane was treated with an excess of 50% potash solution and extracted with benzene. The benzene solution was dried over calcined potash and filtered. A solution of 1.9 g of the dichloride of malonic acid in 10 ml of benzene was added drop by drop to the filtrate, which was placed in an ice bath and stirred. On completion of the addition, the mixture was stirred for another 30 minutes in the cold, and then for 2.5 hours at room temperature, after which 15 ml of a 50% potash solution was added and the oil which separated was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, the chloroform was distilled off and the remaining material distilled in vacuo. 1.2 g (31.9%) of a straw-colored caramel-like mass boiling at 228-229° (0.45 mm) was obtained.

Found %: C 65.04; H 9.15; N 15.88. $C_{19}H_{32}O_2N_4$. Calculated %: C 65.51; H 9.19; N 16.09.

3-Acetyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane. 2.05 g (65%) of this substance in the form of a colorless, oily liquid boiling at 117-118° (0.7 mm) was obtained from 4 g of the dichlorohydrate of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane and 1.5 g of acetyl chloride by the method described above.

Found %: N 15.28, 15.58. $C_{10}H_{18}ON_2$. Calculated %: N 15.38.

Iodomethylate – a white crystalline substance, m.p. 258-260°.

Found %: N 8.29; I 39.19. $C_{11}H_{21}ON_2I$. Calculated %: N 8.64; I 39.19.

Iodohydrate of 9-methyl-9-methyliodide-3,9-diazabicyclo-(3,3,1)-nonane. 2.9 g of the iodomethylate of 3-acetyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane was boiled for three hours with 30 ml of 15% hydriodic acid. The solution was evaporated in vacuo, and the crystalline precipitate remaining was treated three times with anhydrous alcohol and subsequently filtered. 3.3 g (91.6%) of a white crystalline substance, m.p. 265-266°, was obtained.

Found %: N 6.67; I 61.35. $C_9H_{20}N_2I_2$. Calculated %: N 6.83; I 61.95.

Iodomethylate of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane. 3 g of the iodohydrate of 9-methyl-9-methyliodide-3,9-diazabicyclo-(3,3,1)-nonane was heated with 0.29 g of caustic soda in 15 ml of methanol at the boiling point for three hours. The precipitate was filtered off and treated with boiling methanol. 1.83 g (88.8%) of a substance with a m.p. of 245-246° was obtained. The material was in soluble in methyl and ethyl alcohols and in chloroform.

Found %: N 9.40; I 45.22. $C_9H_{19}N_2I$. Calculated %: N 9.92; I 45.03.

3-{β-[9'-Methyl-3',9'-diazabicyclo-(3',3',1')-nonano-3']-propionyl}-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane. 4.3 g of the dichlorohydrate of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane was added, with stirring, to a solution of 2.2 g of caustic soda in 30 ml of anhydrous alcohol. A solution of 4.3 g of 3-(β-chloropropionyl)-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane [1] in 30 ml of anhydrous alcohol was also added and the reaction mixture heated for 3.5 hours at 60° (on a bath). The alcohol was distilled off in vacuo and the remaining material treated with an excess of a 50% potash solution and extracted with ether. The ether extract was dried over calcined sodium sulfate, the solvent distilled off and the residue distilled in vacuo. 2.45 g (39.5%) of a colorless, slightly mobile liquid with a b.p. of 203-205° (0.8 mm) was obtained.

Found %: C 67.72; H 10.14; N 16.73. $C_{19}H_{34}ON_4$. Calculated %: C 68.26; H 10.17; N 16.76.

1,3-Bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-propane. 3.3 g of 3-β-[9'-methyl-3',9'-diazabicyclo-(3',3',1')-nonano-3']-propionyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane was reduced with 0.4 g of lithium alumi-

num hydride in an etherbenzene solution. 2.45 g (77.5%) of a colorless, oily liquid boiling at 162-163° (0.3 mm) was obtained.

Found %: C 71.03; H 11.21; N 17.70. $C_{19}H_{36}N_4$. Calculated %: C 71.25; H 11.25; N 17.50.

The diiodomethylate is a white substance with fine crystals, m.p. 247-249°.

Found %: N 9.51; I 41.82. $C_{21}H_{42}N_4I_2$. Calculated %: N 9.27; I 42.05.

The dimethylsulfomethylate is a white crystalline substance, m.p. 172-174°.

Found %: N 9.48; S 11.02. $C_{23}H_{48}O_8N_4S_2$. Calculated %: N 9.79; S 11.18.

1,2-Bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-ethane. A solution of 3.46 g of caustic soda in 10 ml of water was added to a solution of 10 g of the dichlorohydrate of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane in 25 ml of water at a temperature not to exceed 5°; then the solution was cooled to 0° and at this temperature 2.7 g of the chloride of chloroacetic acid and a solution of 1.73 g of caustic soda in 5 ml of water were added simultaneously drop by drop. On completion of the addition, the reaction mixture was stirred for another ten minutes and then 15 ml of a 50% solution of potash was added and the mixture extracted with ether. The ether extract was dried over calcined sodium sulfate, the ether was distilled off, and the 3-{[9'-methyl-3',9'-diazabicyclo-(3',3',1')-nonano-3']-acetyl}-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane, in the form of a light-brown caramel-like mass, was reduced by means of 1 g of lithium aluminum hydride in a mixture of ether and dioxane. 2.45 g of a colorless, slightly mobile liquid with a b.p. of 162-164° (0.7 mm) was obtained. The yield was 45% based on the undistilled amide.

Found %: C 69.71; H 11.08; N 17.95. $C_{18}H_{34}N_4$. Calculated %: C 70.58; H 11.11; N 18.30.

The diiodomethylate was a fine white crystalline substance, m.p. 256-258°.

Found %: N 9.30; I 42.85. $C_{20}H_{40}N_4I_2$. Calculated %: N 9.49; I 43.05.

The dimethylsulfomethylate was a white crystalline substance, m.p. 220-222°.

Found %: N 9.94; S 11.26. $C_{22}H_{46}O_8N_4S_2$. Calculated %: N 10.00; S 11.46.

SUMMARY

For the purpose of pharmacological study, diquaternary salts of 1,3-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-propane and 1,2-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]-ethane were synthesized with methyl iodide and dimethylsulfate.

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UNSATURATED HYDROCARBONS

XIV. SYNTHESIS OF POLYCYCLIC HYDROCARBONS BY THE DEHYDRO-CYCLIZATION OF ACETYLENE DERIVATIVES

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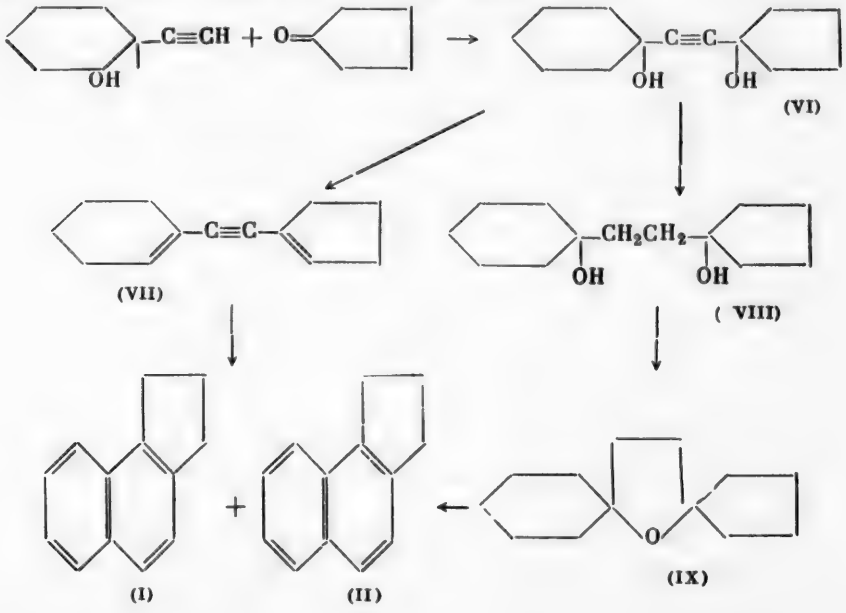
Although the dehydrocyclization of hydrocarbons on oxide catalysts was discovered not less than a quarter of a century ago [1], the overwhelming majority of investigations in this field has been devoted to the synthesis only of monocyclic aromatic hydrocarbons. The synthesis of polycyclic aromatic hydrocarbons by this method is limited to only isolated examples [2].

In recent years, a series of communications has been published from our laboratory [3] in which the possibility of synthesizing polycyclic aromatic hydrocarbons by another method – the dehydrocyclization of acetylenic glycols and their conversion products (by hydrogenation and dehydration) – has been shown.

The present work is devoted to the development of these investigations and deals with the synthesis of tri- and tetracyclic condensed aromatic hydrocarbons, its special feature being that the possibility here shown of obtaining hydrocarbons of these classes containing a five-membered ring by catalytic dehydrocyclization. As is known, the synthesis of such substances presents considerable difficulty, involves many stages, and requires extremely complex starting materials [4].

In the communication, we report the synthesis of the following compounds: 1,2-cyclopentenonaphthalene (I), 1,2-$\Delta^{2',3'}$-cyclopentadienonaphthalene (II), 1,2-cyclopentenophenanthrene (III), and 1,2-$\Delta^{1',2'}$- (or -$\Delta^{2',3'}$-)-cyclopentadienophenanthrene (IV), and chrysene (V).

We obtained 1,2-cyclopentenonaphthalene (I) and the 1,2-cyclopentadienonaphthalene starting from ethinylcyclohexanol and cyclopentanone according to the following scheme.

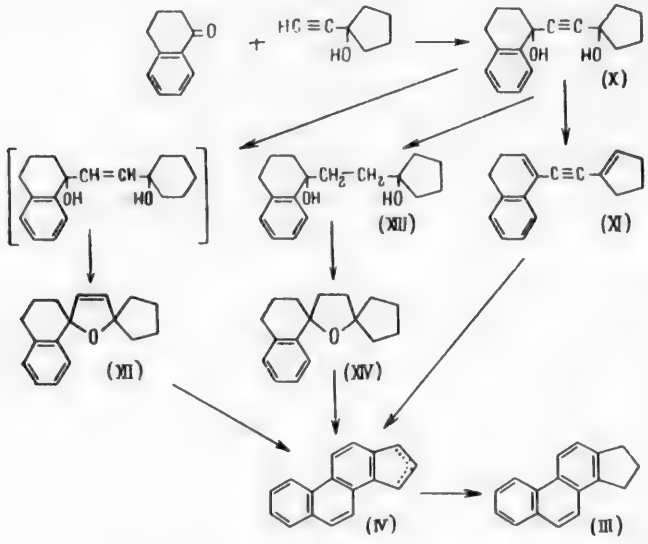


The condensation of ethinylcyclohexanol and cyclopentanone by Iotsich's method gave a good yield of 1-(1'-hydroxycyclohexyl)-2-(1"-hydroxycyclopentyl)-acetylene (VI) which was converted by dehydration in the presence of dilute sulfuric acid into 1-(cyclohex-1'-en-1'-yl)-2-(cyclopent-1"-en-1"-yl)-acetylene (VII). The latter was dehydrocyclized on an aluminum-chromium catalyst promoted with magnesium oxide to form the cyclopentenonaphthalene (I) and the cyclopentadienonaphthalene (II) with a total yield of 26.6%, the amount of (I) formed being approximately twice as much as (II). As we have shown earlier [5], some diminution in the unsaturation of the compounds subjected to aromatization leads to a marked increase in the yield of final product, the best yield of aromatic hydrocarbons being given by dienes and trienes or compounds which are capable of giving hydrocarbons with two or three double bonds on dehydration (potential dienes and trienes).

With this aim, the acetylenic glycol (VI) was hydrogenated to 1-(1'-hydroxycyclohexyl)-2-(1"-hydroxycyclopentyl)-ethane (VIII), which on dehydration with hydrogen chloride in benzene was converted into 2-spirocyclohexyl-5-spirocyclopentyltetrahydrofuran (IX). The latter compound on dehydrocyclization on the same catalyst as was used in the case of the dienyne (VII) forms a mixture of (I) and (II) with a yield of 37.8%, (I) and (II) being obtained in approximately equal amounts. The cyclopentenonaphthalene (I) corresponds to the product obtained previously [4]. The structure of the cyclopentadienonaphthalene (II) was shown by analysis, by the molecular weight, and by the presence in its infrared spectrum of bands corresponding to the bands characteristic for naphthalene derivatives (865, 878, 954 cm^{-1}), a C – H bond in an aromatic nucleus (1388 cm^{-1}) and a C = C in a cyclopentane ring (1587 and 1641 cm^{-1}). The other possible cyclopentadienenonaphthalene, namely 1,2-$\Delta^{1',2}$-cyclopentadienonaphthalene is excluded, since the constants given for it in the literature [6] do not correspond to the product which we obtained.

The ultraviolet and infrared spectra of the cyclopentadienonaphthalene (II) are given in Figs. 1 and 2. The ultraviolet spectra of the compounds (VI-VIII) are given in Fig. 3.

The synthesis of the cyclopentenophenanthrene (III) and the cyclopentadienophenanthrene (IV), which are of interest as substances possessing the cyclic hydrocarbon skeleton of the steroid hormones was effected according to the following scheme.



The reaction of 1-ethinylcyclopentanol with α-tetralone by Iotsich's method takes place slowly, but on prolonged stirring of the reaction mixture, 1-(1-hydroxy-1',2',3',4'-tetrahydronaph-1'-yl)-2-(1"-hydroxycyclopent-1"-yl)-acetylene (X) was formed in satisfactory yield. On stirring the diol (X) with 30% sulfuric acid, it dehydrates with the formation of 1-(3',4'-dihydronaphth-1'-yl)-2-(cyclopent-1"-en-1"-yl)-acetylene (XI), and the latter, on dehydrocyclization on a promoted aluminum – chromium catalyst is converted into the cyclopentadienophenanthrene (IV) with a yield of only 5.3%. However, in the aromatization of 2-spiro-(1',2',3',4'-tetrahydronaph-1'-yl)-5-spirocyclopentyltetrahydrofuran (XIV), which is readily synthesized by the action of HCl in benzene on 1-(1'-hydroxy-1',2',3',4'-tetrahydronaph-1'-yl)-2-(1"-hydroxycyclopent-1"-yl)-ethane (XIII), obtained by the exhaustive hydrogenation of the diol (X), the cyclopentadienophenanthrene (IV) is formed in a yield of 19.3%. The yield of (IV)

is increased to 34.3% when the dihydrofuran (XII), formed by the partial hydrogenation of the diol (X) and the ready dehydration of the diol (XV) is aromatized. On dehydrocyclizing the dihydrofuran (XII) over the same unregenerated catalyst, the yield of the cyclopentadienophenanthrene (IV) rises to 44.5%. On hydrogenation over a skeletal nickel catalyst, the cyclopentadienophenanthrene (IV) is converted into the cyclopentenophenanthrene (III).

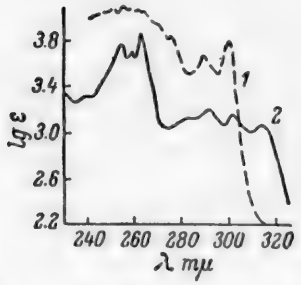
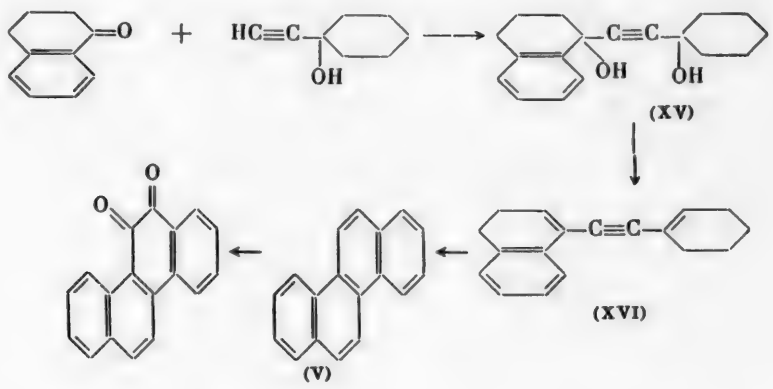


Fig. 1. UV spectra. 1) 1,2-$\Delta^{2',3'}$-cyclopentadienonaphthalene (I); 2) 1,2-$\Delta^{1',2'}$- (or -$\Delta^{2',3'}$-)-cyclopentadienophenanthrene (IV).

The structure of the cyclopentadienophenanthrene (IV) was shown by analysis, by the molecular weight, and by the infrared spectrum, in which bands were found characteristic for the phenanthrene nucleus (778, 829, and 864 cm^{-1}), for the C – H bond in aromatic hydrocarbons (1398 cm^{-1}), and for the C = C bond in a cyclopentane ring (1580 and 1616 cm^{-1}), and also by the agreement of its melting point with data in the literature. The position of the double bond in the cyclopentane ring was not determined.

The infrared and ultraviolet spectra of the cyclopentadienophenanthrene (IV) are shown in Figs. 4 and 1, and the ultraviolet spectra of the diols (X) and (XIII) and the furans (XII) and (XIV) are given in Figs. 5 and 6.

Chrysene (V) was synthesized in a similar manner, starting from α-tetralone and 1-ethinylcyclohexan-1-ol.



The condensation of α-tetralone with 1-ethinylcyclohexan-1-ol by Iotsich's method leads to 1-(1'-hydroxy-1',2',3',4'-tetrahydronaph-1'-yl)-2-(1"-hydroxycyclohex-1"-yl)-acetylene (XV), which, on distillation with p-toluenesulfonic acid forms 1-(3',4'-dihydronaph-1'-yl)-2-(cyclohex-1"-en-1"-yl)-acetylene (XVI). The latter was aromatized to form chrysene (V) with a yield of 34.3%.

The oxidation of the chrysene with chromic anhydride in acetic acid gave chrysoquinone.

Compounds similar to those synthesized in the present work have recently been attracting the attention of chemists for the study of the nature of semi-conductor catalysis. From this point of view, the present work is of interest as giving a general method for the directed synthesis of polycyclic aromatic hydrocarbons.

The authors express their thanks to N. I. Shergina and E. I. Kositsyna for assistance in taking the IR spectra.

EXPERIMENTAL

1-(1'-Hydroxycyclohexyl)-2-(1"-hydroxycyclopentyl)-acetylene (VI) and its dehydration. a) A solution of 62 g of ethinylcyclohexanol (m.p. 31-32°) in 15 ml of ether was added over 20 min to a solution of the magnesium ethyl bromide from 24.3 g of magnesium and 115 g of ethyl bromide in 0.5 liter of ether, and after 10 min 41 g of cyclopentanone was added, and the mixture was stirred for a further 3 hours and left overnight. The reaction mass was decomposed with 150 ml of water and 100 ml of hydrochloric acid (1 : 1). The ethereal layer was washed with sodium bicarbonate solution and dried over potash. The ether was distilled off and 80 g (77.6%) of the diol (VI) with m.p. 92-93° (from alcohol) [7] was obtained.

b) Fifty grams of the diol (VI) in 75 g of 40% sulfuric acid was heated on the boiling water bath for 2 hours and was then cooled, and the material was extracted with ether. On distillation, 20 g (47.4%) of 1-(cyclohex-1'-en-1'-yl)-2-(cyclopent-1"-en-1"-yl)-acetylene (VII) was obtained, with b.p. 113-116° (3 mm), n^{20}_D 1.5590 [7].

Hydrogenation of the diol (VI). A solution of 130 g of the diol in 130 ml of alcohol was hydrogenated over a skeletal nickel catalyst at 100° and an initial pressure of 70 atm until the absorption of hydrogen ceased. After distilling off the alcohol, 128 g (~ 97%) of 1-(1'-hydroxycyclohexyl)-2-(1"-hydroxycyclopentyl)-ethane (VIII) with m.p. 97.5-98° (from benzene) was obtained.

Found %: C 73.01, 73.07; H 11.45, 11.59. $C_{13}H_{24}O_2$. Calculated %: C 73.53; H 11.40.

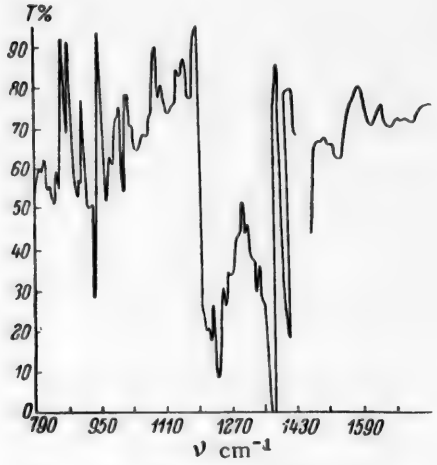


Fig. 2. The IR spectrum of 1,2-$\Delta^{2',3'}$- cyclopentadienonaphthalene (II).

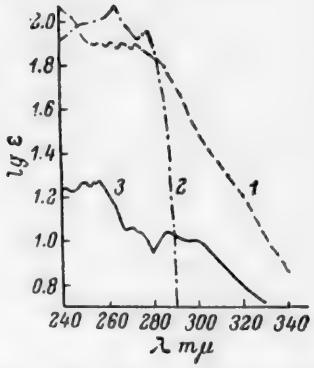


Fig. 3. UV spectra. 1) 1-(1'-Hydroxycyclohexyl)-2-(1"-hydroxycyclopentyl)-acetylene (VI); 2) 1-(cyclohex-1'-en-1'-yl)-2-(cyclopent-1"-en-1"-yl)-acetylene (VII); 3) 1-(1'-hydroxycyclohexyl)-2-(1"-hydroxycyclopentyl)-ethane (VIII).

Dehydration of the diol (VIII). Dry hydrogen chloride was passed through a mixture of 20 g of the glycol (VIII) and 150 ml of benzene. The passage of the gas was discontinued 5 minutes after the appearance of an aqueous layer on the bottom of the flask. The benzene layer was washed with sodium bicarbonate solution and water, and was dried with calcium chloride. On distilling 100 g of the dehydration products in a column, 42.5 g of 2-spirohexyl-5-spirocyclopentyltetrahydrofuran (IX) was isolated. On standing over sodium, the furan (IX) did not change.

B. p. 70-72° (1 mm), n_D^{20} 1.7787, d_4^{20} 0.9641, MR_D 57.40; calc. 57.18.

Found %: C 80.62; H 11.44. $C_{13}H_{22}O$. Calculated %: C 80.35; H 11.41.

The aromatization of 1-(cyclohex-1'-en-1'-yl)-2-(cyclopent-1"-en-1"-yl)-acetylene (VII) was carried out over 50 ml of a $MgO(Cr_2O_3)Al_2O_3$ (2 : 18 : 80) catalyst in the continuous flow apparatus described previously [8]. Before the commencement and at the end of the experiment, hydrogen was passed through the system. The initial substance was fed in the form of a 46% solution in benzene. The benzene was distilled off from the catalyzate, and the residue was distilled from a Claisen flask. A semi-crystalline mass with b.p. 98-102° (1 mm) was obtained, and separate substances were isolated from it with alcohol. After recrystallizing 14 g of this mass obtained under the conditions of experiment No. 5 (see Table) from alcohol, 9 g of the 1,2-cyclopentenonaphthalene (I) was obtained, with b.p. 110-110.5° (1.5 mm); picrate m.p. 104.5-106°.

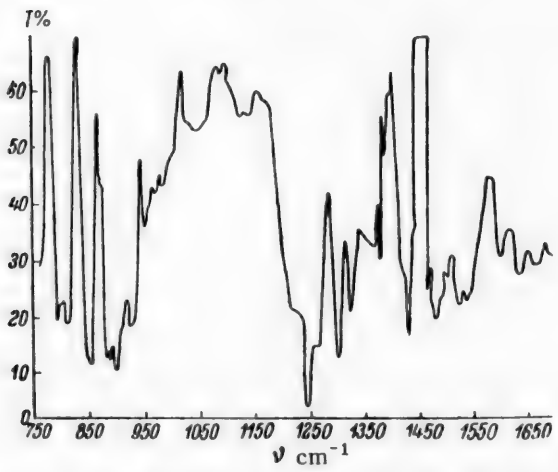


Fig. 4. The IR spectrum of 1,2-$\Delta^{1',2'}$- (or -$\Delta^{2',3'}$-)-cyclopentadienophenanthrene (IV).

Found %: C 92.68; H 7.25. $C_{13}H_{12}$. Calculated %: C 92.81; H 7.19.

Literature data [4]: b.p. 90-100° (0.04 mm); picrate m.p. 105-106°.

Principle maxima: 270, 276, 280, 285, 291, 309, and 317 mμ; log ε 3.55, 3.61, 3.62, 3.59, 3.55, 3.13,

3,02; and minima: 271, 277, 290, 307, 313, and 320 mμ; log ε 3.52, 3.59, 3.54, 3.02, 2.97, and 2.78. The UV absorption spectra of the cyclopentenonaphthalene in alcohol agree with those given in the literature [8].

In addition, 5 g of the 1,2-$\Delta^{2',3'}$-cyclopentadienonaphthalene (II) with m.p. 111.5-112.5° (from alcohol) was obtained.

Found %: C 93.51; H 6.13. M 165.8. $C_{13}H_{10}$. Calculated %: C 93.94; H 6.06. M 116.

The IR spectrum is given in Fig. 2 and the UV spectrum in Fig. 1.

The results of the experiments on the aromatization of the dienyne (VII) are given in the table.

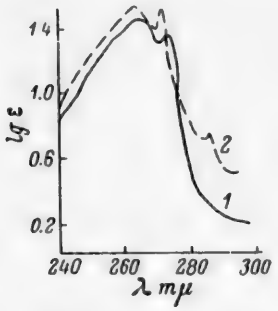


Fig. 5. UV spectra. 1) 1-(1'-Hydroxy-1',2',3',4'-tetrahydronaph-1'-yl)-2-(1"-hydroxycyclopent-1"-yl)-acetylene (X); 2) 1-(1'-hydroxy-1',2',3',4'-tetrahydronaph-1'-yl)-2-(1"-hydroxycyclopent-1"-yl)-ethane (XIII).

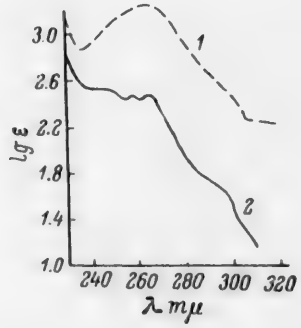


Fig. 6. UV spectra. 1) 2-spiro-(1',2',3',4'-tetrahydronaph-1'-yl)-5-spirocyclopentyl-dihydrofuran (XII); 2) 2-spiro-(1',2',3',4'-tetrahydronaph-1'-yl)-5-spirocyclopentyl-tetrahydrofuran (XIV).

The aromatization of the furan (IX) was carried out in a similar manner to that described above for the aromatization of the dienyne (VIII). On recrystallizing 9.5 g of a fraction with m.p. 112-122° (12 mm) obtained under the conditions of experiment No. 8 from alcohol, 5.5 g of the 1,2-cyclopentenonaphthalene (I) with b.p. 104-106° (1 mm), picrate m.p. 104-105° (from alcohol), and 4 g of the 1,2-$\Delta^{2',3'}$-cyclopentadienonaphthalene (II) with m.p. 113-114° (from alcohol) were obtained. The results of the experiments are given in the table.

1-(1'-Hydroxy-1',2',3',4'-tetrahydronaph-1'-yl)-2-(1"-hydroxycyclopent-1"-yl)-acetylene (X). To the ethylmagnesium bromide from 24.3 g of magnesium and 115 g of ethyl bromide was added 60 g of ethinylcyclopentanol (m.p. 20°, b.p. 157°) and on the following day, 75 g of α-tetralone (b.p. 105-107° at 2 mm, $n^{20}D$ 1.5665). Stirring was continued for 3 days at 18°. The reaction mixture was decomposed with 200 ml of water and then with 300 ml of 6% sulfuric acid. The glycol (X) separating out was filtered off, and washed with 3% sulfuric acid and water. A yield of 45 g (36.2%) of the diol (X) with m.p. 155-157° (from alcohol) was obtained.

Found %: C 79.67; H 8.03. $C_{17}H_{20}O_2$. Calculated %: C 79.66; H 7.87.

Hydrogenation of the diol (X). A solution of 60 g of the glycol (X) in 500 ml of alcohol was hydrogenated over a skeletal nickel catalyst at 18° and an initial pressure of 35 atm until the absorption of hydrogen ceased. After the alcohol had been distilled off, 40 g (62.6%) of 1-(1'-hydroxy-1',2',3',4'-tetrahydronaph-1'-yl)-2-(1"-hydroxycyclopent-1"-yl)-ethane (XIII) with m.p. 112-114° (from alcohol) was obtained.

Found %: C 78.47; H 9.45. $C_{17}H_{24}O_2$. Calculated %: C 78.41; H 9.29.

Dehydration of the diol (X). A mixture of 5 g of the glycol (X) and 30 g of 40% sulfuric acid was heated on the boiling water bath for 1.5 hours. After the usual working up, 3.1 g (72%) of 1-(3',4'-dihydronaph-1'-en-1'-yl)-2-(cyclopent-1"-en-1"-yl)-acetylene (XI) with b.p. 168-169° (3 mm), $n^{20}D$ 1.6248, was obtained.

Dehydration of the diol (XIII). Hydrogen chloride was passed through a solution of 10 g of the diol (XIII) in 100 ml of benzene at 18° until an aqueous layer appeared on the bottom of the flask. After the benzene layer had

Synthesis of a Cyclopentenonaphthalene, a Cyclopentadienonaphthalene, a Cyclopentenophenanthrene, and Chrysene by the Dehydrocyclization of Derivatives of Acetylinic Alcohols

Experiment No.	Starting material	Temperature of experiment	Rate of feed (kg/liter of cat./hr)	Amount of initial substance fed	Reaction product: compound	Reaction product: total yield in %
1	(VII)	400°	0.19	7.88	Cyclopentenonaphthalene and cyclopentadienonaphthalene	26.6
2	(VII)	432	0.19	7.60	The same	17.8
3	(VII)	450	0.285	7.60	" "	16.4
4	(VII)	375	0.19	7.88	" "	24.4
5	(VII)	400	0.19	74.40	" "	21.1
6	(IX)	400	0.19	7.3	Cyclopentenonaphthalene and cyclopentadienonaphthalene	16.1
7	(IX)	450	0.285	6.01	The same	30.0
8	(IX)	450	0.19	7.9	" "	37.8
9	(IX)	500	0.380	6.16	" "	25.7
10	(XI)	400	0.3	5.35	Cyclopentadienophenanthrene	4.1
11	(XI)	430	0.3	5.2	" "	5.3
12	(XIV)	400	0.2	7.3	" "	19.3
13	(XIV)	500	0.3	6.13	" "	11.0
14	(XIV)	550	0.7	7.0	" "	—
15	(XII)	400	0.2	7.5	" "	34.3
16	(XII)	400	0.2	4.7	" "	44.5
17	(XVI)	400	0.2	6.0	Chrysene	20.0
18	(XVI)	450	0.2	7.0	" "	31.0
19	(XVI)	500	0.2	6.0	" "	34.3

Experiments Nos. 3, 6, and 16 were carried out over an unregenerated catalyst. In experiment Nos. 4, 5, and 8-19, the material was fed in solution in benzene. In experiments Nos. 10 and 11, 25 ml of catalyst was used.

been washed with sodium bicarbonate and the benzene had been distilled off, the residue was distilled. A yield of 7.6 g (77.2%) of 2-spiro-(1',2',3',4'-tetrahydronaph-1'-yl)-5-spirocyclopentyltetrahydrofuran (XIV) with b.p. 141-143° (1 mm), n^{20}_D 1.5541, was obtained. On standing over sodium, the furan (XIV) underwent no change.

Found %: C 84.10; H 9.14. $C_{17}H_{22}O$. Calculated %: C 84.28; H 9.15.

2-Spiro-(1',2',3',4'-tetrahydronaph-1'-yl)-5-spirocyclopentyldihydrofuran (XII). A solution of 10 g of the diol (X) in 100 ml of alcohol was hydrogenated over skeletal nickel at 18°C until 1 mole of hydrogen had been absorbed. The amount of hydrogen absorbed was 974 ml (theoretical, 1019 ml). The alcohol was distilled off, and the residue was dehydrated in a similar manner to the diol (XIII) (or was distilled with 0.5 g of orthophosphoric acid). A yield of 6.5 g (60%) of the dihydrofuran (XII) was obtained. On standing over sodium, the furan (XII) underwent no change.

B.p. 133.5-134.5° (0.5 mm), n^{20}_D 1.5665, d_4^{20} 1.0626, MR_D 72.480; calc. 71.681.

Found %: C 84.71; H 8.31. $C_{17}H_{20}O$. Calculated %: C 84.97; H 8.39.

Aromatization of the dienyne (XI), the tetrahydrofuran (XIV), and the dihydrofuran (XII). The aromatization was carried out by the method described for the dienine (VII) over a $MgO(Cr_2O_3)Al_2O_3$ (2 : 18 : 80) catalyst. The end product isolated was 1,2-$\Delta^{1',2'}$- (or -$\Delta^{2',3'}$-)-cyclopentadienophenanthrene (IV) with m.p. 182-182.5° (from alcohol).

Found %: C 94.38; H 5.58. M 214.6. $C_{17}H_{12}$. Calculated %: C 94.48; H 5.59. M 216.

Literature data [4]: m.p. 182-183°.

The UV spectrum is given in Fig. 1 and the IR spectrum in Fig. 4.

All results on aromatization are given in the table.

Hydrogenation of 1,2-$\Delta^{1',2'}$- (or -$\Delta^{2',3'}$-)-cyclopentadienophenanthrene (IV). A solution of 1 g of the cyclopentadienophenanthrene (IV) in 500 ml of alcohol was hydrogenated for 3 days in a rotating autoclave over skeletal

nickel at 18° and with an initial pressure of 20 atm. The alcohol was distilled off, and the cyclopentenophenanthrene (V) with m.p. 134-135° (from alcohol) [10] was obtained.

1-(1'-Hydroxy-1',2',3',4'-tetrahydronaph-1'-yl)-2-(1"-hydroxycyclohexyl)-acetylene (XV). To the ethylmagnesium bromide from 24.3 g of magnesium and 115 g of ethyl bromide were added 64 g of 1-ethinylcyclohexanol and, after 20 hours, 75 g of α-tetralone, and the mixture was stirred for a day longer. The mass was subsequently decomposed with 100 ml of water and the ethereal solution poured off the precipitate, which was dissolved in 200 ml of hydrochloric acid (1 : 1) after the addition of ether to it. A yield of 88 g (63.7%) of the diol (XV) with m.p. 105-106° (from alcohol) was obtained; the substance crystallizes on further heating and melts again at 118-120°.

Found %: C 80.07; H 8.09. $C_{18}H_{22}O_2$. Calculated %: C 79.95; H 8.20.

Literature data [9]: m.p. 85-95°.

Dehydration of the diol (XV). Twelve grams of the glycol were rapidly distilled with 2 g of p-toluenesulfonic acid. Redistillation of the hydrocarbon layer, dried with calcium chloride, yielded 3 g (28.8%) of 1-(3',4'-dihydronaph-1'-yl)-2-(cyclohex-1"-en-1"-yl)-acetylene (XVI) with b.p. 170-171° (2 mm), n^{20}_D 1.6180 [9].

Aromatization of 1-(3',4'-dihydronaph-1'-yl)-2-(cyclohex-1"-en-1"-yl)-acetylene (XVI). Aromatization of the dienyne (XVI) to form chrysene (V) was carried out over 50 ml of $Mg(Cr_2O_3)Al_2O_3$ (2 : 18 : 80) catalyst. The dienyne (XVI) was fed to the tube in solution in benzene. The last traces of the catalyzate were displaced from the tube by passing benzene. The benzene was distilled off and the substance was crystallized from alcohol, chrysene with m.p. 252° [10] being obtained.

Principle maxima: 242, 260, 268, 296 mμ; log ε 4.39, 4.92, 4.27, 4.25; and minima; 244, 262, 290,300 mμ; log ε 4.38, 4.88, 4.21, 4.13. The UV absorption spectra of chrysene in decalin agreed with those given in the literature [11].

Data on the aromatization of the dienyne (XVI) are given in the table.

Oxidation of chrysene (V). A solution of 1 g of chrysene in 30 ml of glacial acetic acid was heated for 2 hours on the boiling water bath with 2.5 g of chromic anhydride in 20 ml of glacial acetic acid; after cooling, an orange precipitate formed which was separated off and washed with water. It consisted of chrysoquinone with m.p. 235-237° (from alcohol) [10].

SUMMARY

1. The suitability of the dehydrocyclization reaction for the directed synthesis of polycyclic aromatic hydrocarbons has been shown.

2. The possibility of synthesizing polycyclic aromatic hydrocarbons with condensed cyclopentane rings by this method has been shown.

3. On the basis of tri- and tetracyclic aromatic hydrocarbons with condensed rings, the generality of the method previously proposed by the authors for the synthesis of aromatic hydrocarbons with a given structure from acetylenic compounds has been demonstrated.

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THE CHEMISTRY OF UNSATURATED ETHERS

VI. THE CONDENSATION OF ACETALS WITH 1-ALKOXYDIENES

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It has recently been shown that 1-ethoxybutadiene and 1-ethoxyisoprene (1-ethoxy-3-methylbutadiene) are capable of adding acetals of α,β-unsaturated aldehydes in the 1,4 positions [1, 2]. This reaction is a new convenient method for lengthening a hydrocarbon chain.

It was of interest to study the reaction of acetals with various substituted 1-alkoxydienes. In the present work, the addition of the diethyl acetal of crotonaldehyde (I) to 1-ethoxy-2-methylbuta-1,3-diene (II, $R_1 = H$, $R_2 = CH_3$) and 1-ethoxy-2,3-dimethylbuta-1,3-diene (III, $R_1 = R_2 = CH_3$) [3] has been studied. A 10% solution of zinc chloride in ethyl acetate was used as catalyst. In all the cases which we studied, the acetal of crotonaldehyde added to the 1-alkoxydiene in the 1,4-positions.

Since the addition of acetals to 1-alkoxydienes forms alkoxyacetals of α,β-unsaturated aldehydes which, in their turn, are also capable of adding to 1-alkoxydienes, a mixture of products of the addition of one, two, three, etc., molecules is obtained in the reaction, the components of which are readily separated by fractional distillation.

The mechanism of these additions may be represented in the following way.

$$\underset{(I)}{CH_3-CH=CH-CH\langle^{OC_2H_5}_{OC_2H_5}} + ZnCl_2 \rightleftarrows$$

$$\rightleftarrows \underset{(III)}{[CH_3-CH=CH-\overset{+}{C}H-OC_2H_5]} + \underset{(IV)}{[ZnCl_2\bar{O}C_2H_5]}$$

$$(III) + \underset{(II)}{CH_2=\overset{R_1}{C}-\overset{R_2}{C}=CH-OC_2H_5} \rightarrow$$

$$\rightarrow \left[\underset{(V)}{CH_3-CH=CH-\overset{OC_2H_5}{\overset{|}{C}H}-CH_2-\overset{R_1}{\overset{|}{C}}=\overset{R_2}{\overset{|}{C}}-\overset{+}{C}H-OC_2H_5}\right] \xrightarrow{n(II)}$$

$$\rightarrow \left[\underset{(VI)}{CH_3-CH=CH-\left(\overset{OC_2H_5}{\overset{|}{C}H}-CH_2-\overset{R_1}{\overset{|}{C}}=\overset{R_2}{\overset{|}{C}}\right)_n-\overset{+}{C}H-OC_2H_5}\right] \xrightarrow{(IV)}$$

$$\rightarrow \underset{(VII)}{CH_3-CH=CH-\left(\overset{OC_2H_5}{\overset{|}{C}H}-CH_2-\overset{R_1}{\overset{|}{C}}=\overset{R_2}{\overset{|}{C}}\right)_n-CH\langle^{OC_2H_5}_{OC_2H_5}} + ZnCl_2$$

When Lewis acids (BF_3, $ZnCl_2$, $FeCl_3$, etc.) react with acetals, the intermediate carbonium ion (III) is formed by the withdrawal of the free electron pair of the oxygen atom of an acetal alkoxyl group. The carbonium ion (III) adds to the molecule of alkoxydiene forming a new carbonium ion (V) which, in its turn, is also capable of adding the alkoxydiene (II) and forming a new carbonium ion (VI), and so on. When the carbonium ions (V) or (VI) react with an anion (IV) an unsaturated alkoxyacetal (VII) is formed and the $ZnCl_2$ is regenerated.

The 1-alkoxydienes are also activated by Lewis acids, which considerably intensify the shift of the electron density of the system of conjugated bonds of the molecule, thus leading to an increased reactivity in addition reactions.

Thus, the addition of acetals to 1-alkoxydienes can be regarded as a stepwise polymerization of the 1-alkoxydienes. The degree of this polymerization depends on the ratio of the acetal and the alkoxydiene used in the reaction. In order to diminish the yield of products of repeated addition, we used a two-fold excess of the diethylacetal of crotonaldehyde. Nevertheless, the reaction yielded products of primary, secondary, tertiary, and quaternary addition, which were isolated in the pure form by fractional distillation.

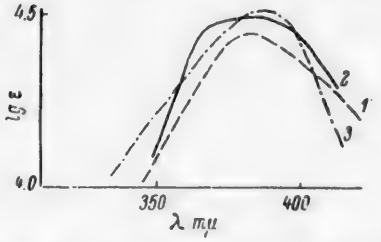

Fig. 1. UV absorption spectra of the 2,4-dinitrophenylhydrazones of the alkoxyaldehydes (VIII). 1) (VIII), R_1 = = H, R_2 = CH_3, n = 1, λ_{max} (in alcohol), 383 mμ, ε = 27000; 2) (VIII), R_1 = H, R_2 = CH_3, n = 2, λ_{max} (in alcohol), 385 mμ, ε 30800; 3) (VIII), R_1 = H, R_2 = CH_3, n = 3, λ_{max} (in alcohol), 388 mμ, ε = 32000.

To prove the direction of the reaction (in the 1,2 or 1,4 positions) the alkoxyacetals obtained (VII) were converted by the action of dilute phosphoric acid into the corresponding unsaturated aldehydes (VIII) with yields of 87-95%.

$$(VII) \longrightarrow CH_3-CH=CH-\underset{(VIII)}{\left(CH(OC_2H_5)-CH_2-C(R_1)=C(R_2)\right)_n}-CHO$$

It was found that the alkoxyaldehydes obtained (VIII) are α, β-unsaturated aldehydes, this being shown by means of the UV absorption spectra of their 2,4-dinitrophenylhydrazones (see Fig. 1).

All the 2,4-dinitrophenylhydrazones of the alkoxyaldehydes obtained (VIII) have an intense absorption band in the 383-388 mμ region, which is characteristic for α, β-unsaturated aldehydes, and no absorption bands at 350-360 mμ, corresponding to saturated aldehydes, were found [4]. This shows that in our case the addition goes in the 1,4 positions.

The alkoxyaldehydes (VIII), on boiling in toluene in the presence of acidic catalysts (H_3PO_4, $NH_4H_2PO_4$, p-$CH_3C_6H_4SO_3H$), are capable of splitting out alcohol with the formation of polyenic aldehydes (IX).

$$(VIII) \longrightarrow CH_3-CH=CH-\underset{(IX)}{\left(CH=CH-C(R_1)=C(R_2)\right)_n}-CHO.$$

2-Methylocta-2,4,6-trienal (IX, R_1 = H, R_2 = CH_3, n = 1) was obtained by this method from (VIII, R_1 = H, R_2 = = CH_3, n = 1) in the presence of H_3PO_4. The 2,4-dinitrophenylhydrazone of this aldehyde has the characteristic absorption bands for trienals, which proves its structure [4].

Crystalline 2,6-dimethyldodeca-2,4,6,8,10-pentaenal (IX, R_1 = H, R_2 = CH_3, n = 2) and 2,3,6,7-tetramethyldodeca-2,4,6,8,10-pentaenal (IX, R_1 = R_2 = CH_3, n = 2) were obtained in a similar manner in the presence of $NH_4H_2PO_4$ and p-toluenesulfonic acid. The structure of these compounds was shown by their UV absorption spectra which have the characteristic absorption bands for pentaenals [4].

EXPERIMENTAL

Addition of diethyl acetal of crotonaldehyde (I) to 1-ethoxy-2-methylbuta-1,3-diene (II, R_1 = H, R_2 = CH_3). The addition of 43.5 g of 1-ethoxy-2-methylbuta-1,3-diene to a mixture of 120 g of the diethyl acetal of crotonaldehyde and 18 ml of a 10% solution of zinc chloride in ethyl acetate was carried out at 45° in a current of dry nitrogen with stirring. The mixture was stirred at the same temperature for a further 7 hours and was then cooled, neutralized with sodium ethoxide, diluted with ether, washed with water, and dried with sodium sulfate. After two vacuum distillations, the following fractions were obtained: 1st – 59.1 g of the initial diethyl acetal of crotonaldehyde with b.p. 48° (12 mm), $n^{20}D$ 1.4104; 2nd – 47.3 g of 1,1,5-triethoxy-2-methylocta-2,6-diene (VII, R_1 = H, R_2 = CH_3, n = 1); 3rd – 23.2 g of 1,1,5,9-tetraethoxy-2,6-dimethyldodeca-2,6-10-triene (VII, R_1 = H, R_2 = CH_3, n = 2); 4th – 9.4 g of 1,1,5,9,13-pentaethoxy-2,6,10-trimethylhexadeca-2,6,10,14-tetraene (VII, R_1 = H, R_2 = CH_3, n = 3); 5th – 3.0 g of 1,1,5,9,13,17-hexaethoxy-2,6,10,14-tetramethyleicosa-2,6,10,14,18-pentaene (VII, R_1 = H, R_2 = CH_3, n = 4).

TABLE 1. Ethoxyacetals (VII)

$$CH_3-CH=CH-\left(\begin{matrix}OC_2H_5 & R_1 & R_2\\ | & | & |\\ CH-CH_2-C=C\end{matrix}\right)_n-CH(OC_2H_5)_2$$

Serial No.	R_1	R_2	n	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Empirical formula	Found % C	Found % H	Calculated % C	Calculated % H	Yield %
1	H	CH_3	1	72° (0.025)	1.4415	0.9020	75.09	75.46	$C_{15}H_{28}O_3$	70.14, 70.29	10.95, 10.89	70.27	11.01	48
2	H	CH_3	2	125 (0.07)	1.4580	0.9255	108.63	108.91	$C_{22}H_{40}O_4$	71.94, 71.86	10.95, 10.82	71.67	10.94	32.5
3	H	CH_3	3	158—160 (0.035)	1.4678	0.9367	142.63	142.45	$C_{29}H_{52}O_5$	72.32, 72.74	10.94, 10.93	72.47	10.91	12.2
4	H	CH_3	4	178—180 (0.06)	1.4720	—	—	—	$C_{36}H_{64}O_6$	73.10, 73.22	10.78, 10.79	72.93	10.85	5.7
5	CH_3	CH_3	1	79 (0.11)	1.4580	0.9201	80.19	80.08	$C_{16}H_{30}O_3$	71.13, 70.95	10.90, 10.72	71.07	11.18	25.7
6	CH_3	CH_3	2	120—124 (0.03)	1.4698	0.9303	118.92	118.73	$C_{24}H_{44}O_4$	72.83, 72.83	10.99, 10.91	72.68	11.18	17.3
7	CH_3	CH_3	3	138—140 (0.025)	1.4749	0.9339	156.62	156.37	$C_{32}H_{58}O_5$	73.29, 73.30	10.97, 10.78	73.51	11.18	12.8
8	CH_3	CH_3	4	170—171 (0.03)	1.4812	—	—	—	$C_{40}H_{72}O_6$	73.80, 73.82	11.11, 10.93	74.02	11.18	9.1

By the same method, the diethylacetal of crotonaldehyde (I) and 1-ethoxy-2,3-dimethylbuta-1,3-diene (II, $R_1 = R_2 = CH_3$) yielded: 1,1,5-triethoxy-2,3-dimethylocta-2,6-diene (VII, $R_1 = R_2 = CH_3$, n = 1), 1,1,5,9-tetraethoxy-2,3,6,7-tetramethyldodeca-2,6,10-triene (VII, $R_1 = R_2 = CH_3$, n = 2), 1,1,5,9,13-pentaethoxy-2,3,6,7,10,11-hexamethylhexadeca-2,6,20,14-tetraene (VII, $R_1 = R_2 = CH_3$, n = 3), and 1,1,5,9,13,17-hexaethoxy-2,3,6,7,10,11,14,15-octamethyleicosa-2,6,10,14,18-pentaene (VII, $R_1 = R_2 = CH_3$, n = 4).

The constants of the compounds are given in Table 1.

5-Ethoxy-2-methylocta-2,6-dienal (VIII, $R_1 = H$, $R_2 = CH_3$, n = 1). A mixture of 3.6 g of 1,1,5-triethoxy-2-methylocta-2,6-diene (VII, $R_1 = H$, $R_2 = CH_3$, n = 1), 2 ml of 10% phosphoric acid, and 4 ml of ethanol was heated in an atmosphere of nitrogen for 1 hour. After cooling, the reaction product was neutralized with 5% sodium bicarbonate, diluted with ether, washed with water, dried, and distilled. A yield of 2.45 g of 5-ethoxy-2-methylocta-2,6-dienal (VIII, $R_1 = H$, $R_2 = CH_3$, n = 1) was obtained.

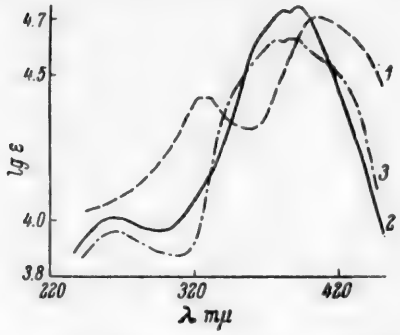

Fig. 2. UV absorption spectra of the polyene aldehydes (IX) 1) 2,4-Dinitrophenylhydrazone of (IX) $R_1 = H$, $R_2 = CH_3$, n = 1, λ_{max} (in alcohol) 323-332 mμ, ε 26000, 408 mμ, ε 51600; 2) (IX), $R_1 = H$, $R_2 = CH_3$, n = 2), λ_{max} (in alcohol), 268 mμ, ε 10300, 383 mμ, ε 52000, 390-396 mμ, ε 53600; 3) 2,4-dinitrophenylhydrazone of (IX, $R_1 = R_2 = CH_3$, n = 2), λ_{max} (in alcohol) 271 mμ, ε 8500, 379 mμ, ε 42000, 385-394 mμ, ε 41700.

5-Ethoxy-2,3-dimethylocta-2,6-dienal (VIII, $R_1 = R_2 = CH_3$, n = 1) was obtained by the same method.

5,9-Diethoxy-2,6-dimethyldodeca-2,6,10-trienal (VIII, $R_1 = H$, $R_2 = CH_3$, n = 2). A mixture of 5.5 g of 1,1,5,9-tetraethoxy-2,6-dimethyldodeca-2,6,10-triene (VII, $R_1 = H$, $R_2 = CH_3$, n = 2), 1.5 ml of 1% phosphoric acid, and 3.5 ml of ethanol was shaken for 10 min until a homogeneous system was formed, after which it was allowed to stand for 3 days. The reaction product was neutralized, washed with water, dried, and distilled. A yield of 4.1 g of 5,9-diethoxy-2,6-dimethyldodeca-2,6,10-trienal (VIII, $R_1 = H$, $R_2 = CH_3$, n = 2) was obtained.

The following compounds were obtained in the same way: 5,9,13-triethoxy-2,6,10-trimethylhexadeca-2,6,10,14-tetraenal (VIII, $R_1 = H$, $R_2 = CH_3$, n = 3), 5,9,13,17-tetraethoxy-2,6,10,14-tetramethyleicosa-2,6,10,14,18-deca-2,6,10-trienal (VIII, $R_1 = R_2 = CH_3$, n = 2), 5,9,13-triethoxy-2,3,6,7,10,11-hexamethylhexadeca-2,6,10,14-tetraenal (VIII, $R_1 = R_2 = CH_3$, n = 3), 5,9,13,17-tetraethoxy-2,3,6,7,10,11,14,15-octamethyleicosa-2,6,10,14,18-pentaenal (VIII, $R_1 = R_2 = CH_3$, n = 4).

The constants of the ethoxyaldehydes are given in Table 2.

2-Methylocta-2,4,6-trienal (IX, $R_1 = H$, $R_2 = CH_3$, n = 1). A mixture of 1.5 g of 5-ethoxy-2-methylocta-2,6-dienal (VIII, $R_1 = H$, $R_2 = CH_3$, n = 1), 50 ml of anhydrous toluene, 0.08 g of phosphoric acid, and 0.05 g of hydroquinone was placed in a Favorskii flask with a 25 cm fractionating column, provided with an inlet for nitrogen and a dropping funnel. The mixture was heated in a current of dry nitrogen at a bath temperature of 135°. As toluene distilled off with alcohol (vapor temperature 100-105°), anhydrous toluene was added to the reaction mixture at such a rate that the volume remained constant. After 2 hours, 30 ml of distillate had been collected and at this point the distillate did not contain alcohol (Chugaev – Zerewitinoff test for active hydrogen). After cooling, the reaction mixture was diluted with ether, washed with 5% sodium carbonate, and water, and dried with sodium sulfate. After vacuum distillation in a current of nitrogen, 0.75 g of 2-methylocta-2,4,6-trienal (IX, $R_1 = H$, $R_2 = CH_3$, n = 1) was obtained in the form of a yellow liquid with b.p. 46° (0.06 mm), n^{20}_D 1.5854. The 2,4-dinitrophenylhydrazone had m.p. 165° (Fig. 2, 1).

Found %: N 18.00, 18.12. $C_{15}H_{16}O_4N_4$. Calculated %: N 17.71.

2,6-Dimethyldodeca-2,4,6,8,10-pentaenal (IX, $R_1 = H$, $R_2 = CH_3$, n = 2). A mixture of 1.4 g of 5,9-diethoxy-2,6-dimethyldodeca-2,6,10-trienal (VIII, $R_1 = H$, $R_2 = CH_3$, n = 2), 50 ml of anhydrous toluene, and 0.1 g of ammonium dihydrogen phosphate was heated in a Favorskii flask at a bath temperature of 135°. As the azeotropic mixture distilled off, toluene was added to the flask so that the volume remained constant. After 40 minutes, the distillation of alcohol ceased. The reaction mixture was cooled, neutralized, and washed with water. After the toluene

TABLE 2. Ethoxyaldehydes (VIII)

$$CH_3-CH=CH-\left(\begin{matrix}OC_2H_5 & R_1 & R_2\\ | & | & |\\ CH-CH_2-C=C\end{matrix}\right)_n--CHO$$

Serial No.	R_1	R_2	n	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	Empirical formula	Found %		Calculated %		Yield %	M.p. of the 2,4-dinitrophenylhydrazones	Empirical formula	% N	
								C	H	C	H				found %	calculated %
1	H	CH_3	1	63—64° (0.05)	1.4683	0.9021	$C_{11}H_{18}O_2$	72.76, 72.41	9.89, 9.97	72.46	9.95	95	157	$C_{17}H_{22}O_5N_4$	15.69, 15.25	15.46
2	H	CH_3	2	106—107 (0.06)	1.4734	0.9305	$C_{18}H_{30}O_3$	73.08, 73.35	9.89, 10.15	73.43	10.27	92.6	95	$C_{24}H_{34}O_6N_4$	11.62, 11.84	11.80
3	H	CH_3	3	160—161 (0.14)	1.4838	0.9439	$C_{25}H_{42}O_4$	73.49, 73.60	10.17, 10.20	73.86	10.41	95.5	83	$C_{31}H_{46}O_7N_4$	9.68, 9.99	9.55
4	H	CH_3	4	160 (0.02)	1.4887	—	$C_{32}H_{54}O_5$	73.98, 74.11	10.20, 10.04	74.09	10.49	87.2	—	—	—	—
5	CH_3	CH_3	1	71 (0.14)	1.4732	0.9179	$C_{12}H_{20}O_2$	73.49, 73.40	10.19, 10.18	73.43	10.27	83	112	$C_{18}H_{24}O_5N_4$	14.86, 15.07	14.89
6	CH_3	CH_3	2	115—118 (0.05)	1.4850	0.9417	$C_{20}H_{34}O_3$	74.44, 74.35	10.43, 10.49	74.49	10.63	86	82—83	$C_{26}H_{38}O_6N_4$	11.26, 11.31	11.15
7	CH_3	CH_3	3	132—135 (0.05)	1.4884	0.9443	$C_{28}H_{48}O_4$	74.73, 74.78	10.55, 10.50	74.95	10.78	88.5	68	$C_{34}H_{52}O_7N_4$	9.03, 8.72	8.91
8	CH_3	CH_3	4	155—160 (0.02)	1.4923	—	$C_{36}H_{62}O_5$	75.64, 75.50	10.85, 10.75	75.21	10.87	83.5	—	—	—	—

had been distilled off, 2 ml of methanol was added to the residue and the mixture was allowed to stand (under nitrogen, at a temperature of −3°) for some days in order to crystallize. A yield of 0.42 g (43.8%) of 2,6-dimethyldodeca-2,4,6,8,10-pentanenal (IX, R_1 = H, R_2 = CH_3, n = 2) in the form of yellow crystals with m.p. 108° (Fig. 2, 2) was obtained.

2,3,6,7-Tetramethyldodeca-2,4,6,8,10-pentaenal (IX, R_1 = R_2 = CH_3, n = 2). A mixture of 1.17 g of 5,9-diethoxy-2,3,6,7-tetramethyldodeca-2,6,10-trienal (VIII, R_1 = R_2 = CH_3, n = 2), 0.1 g of p-toluenesulfonic acid, and 50 ml of toluene was heated in a Favorskii flask at a bath temperature of 135°. To keep the volume of the reaction mixture constant, toluene was added to the reaction flask in proportion as the azeotropic mixture distilled off. After 4 hours, the distillation of alcohol ceased (test for active hydrogen), and the mixture was then cooled, diluted with ether, washed with 5% sodium bicarbonate and water, dried, and distilled in vacuum in a current of nitrogen. A yield of 0.61 g (66%) of 2,3,6,7-tetramethyldodeca-2,4,6,8,10-pentaenal (IX, R_1 = R_2 = CH_3, n = 2) was obtained in the form of a yellow viscous liquid with b.p. 104-106° (0.05 mm), n^{20}_D 1.5940, which crystallized on the addition of methanol to form yellow crystals with m.p. 95-97°. The 2,4-dinitrophenylhydrazone had m.p. 70-71° (Fig. 2, 3).

Found %: N 13.75, 13.95. $C_{22}H_{26}O_4N_4$. Calculated %: N 13.65.

SUMMARY

It has been established that the addition of the diethyl acetal of crotonaldehyde to 1-ethoxy-2-methylbuta-1,3-diene and 1-ethoxy-2,3-dimethylbuta-1,3-diene takes place in the 1,4-positions, leading to a mixture of alkoxyacetals – the products of primary, secondary, tertiary, etc., addition. The mechanism of the reaction has been discussed.

2. The conversion of the alkoxyacetals obtained into α, β-unsaturated alkoxyaldehydes and into polyene aldehydes has been studied.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

SYNTHESIS OF THE ETHYL-Δ^1-p-MENTHEN-8-YL, n-BUTYL-Δ^1-p-MENTHEN-8-YL, p-METHYLCYCLOHEXYL-Δ^1-p-MENTHEN-8-YL, and p-MENTHAN-3-YL-Δ^1-p-MENTHEN-8-YL ACETALS OF ACETALDEHYDE

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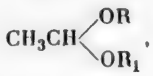
Acetals of acetaldehyde have been synthesized by the interaction of terpineol and vinyl ethers by the Shostakovskii-Gershtein method [1]. In these acetals, having the general formula



R is always the same radical – Δ^1-p-menthen-8-yl and R_1 is a different one: ethyl, n-butyl, p-methylcyclohexyl, or menthan-3-yl.

The α-terpineol was obtained from α-pinene [2] and the vinyl ethers by the Favorskii – Shostakovskii method [3] by the direct interaction of acetylene with ethanol, n-butanol, p-methylcyclohexanol, or menthol.

EXPERIMENTAL

The starting materials for the synthesis of acetals were characterized by the following constants: vinyl ethyl ether: b.p. 35.9°, n^{20}_D 1.3777, d_4^{20} 0.7532; vinyl n-butyl ether: b.p. 93.5°, n^{20}_D 1.4026, d_4^{20} 0.7791; vinyl p-methylcyclohexyl ether: b.p. 165°, n^{20}_D 1.4545, d_4^{20} 0.8860; vinyl p-menthan-3-yl ether: b.p. 166°, n^{20}_D 1.4554, d_4^{20} 0.8720; α-terpineol: b.p. 221°, n^{20}_D 1.4822, d_4^{20} 0.9350.

All the syntheses of the acetals were carried out by the same procedure.

The ethyl Δ^1-p-menthen-8-yl acetal of acetaldehyde. The synthesis was carried out in three-necked flask connected with a reflux condenser and a stirrer provided with a mercury seal. The second neck of the flask bore a thermometer dipping into the reaction mixture, and the catalyst was added through the third. A mixture of 18 g of α-terpineol and 19 g of vinyl ethyl ether was placed in the reaction flask and, with careful stirring, the catalyst – 0.02 ml of concentrated hydrochloric acid – was added. Thereupon the temperature of the reaction mixture rose rapidly, from 15 to 32°. The synthesis was completed when the mixture attained constant room temperature. The hydrochloric acid was neutralized with potash. The acetal was purified with metallic sodium and repeated vacuum distillation from a Favorskii flask. The constants of the main fraction were:

B.p. 110-111° (1 mm), n^{20}_D 1.4602, d_4^{20} 0.9214, MR_D 67.64; calc. 67.47.

Found %: C 74.15, 73.93; H 11.60, 11.65. M 226.76. $C_{14}H_{26}O_2$. Calculated %: C 74.28; H 12.03. M 226.35.

The n-butyl Δ^1-p-menthen-8-yl acetal of acetaldehyde. A mixture of 50 g of α-terpineol and 40 g of vinyl n-butyl ether was used for the synthesis. The catalyst was one drop of concentrated hydrochloric acid. On reaction, the temperature rose from 15 to 28°. The constants of the main fraction, subjected to detailed investigation, were:

B.p. 151-152° (1 mm), n^{20}_D 1.4614, d_4^{20} 0.9081, MR_D 76.79; calc. 76.70.

Found %: C 75.77, 75.67; H 11.75, 11.98. M 254.98. $C_{16}H_{30}O_2$. Calculated %: C 75.53; H 11.88. M 254.40.

The p-methylcyclohexyl Δ^1-p-menthen-8-yl acetal of acetaldehyde. A mixture of 32 g of α-terpineol and 32 g of vinyl p-methylcyclohexyl ether was used for the synthesis. The main fraction had:

B.p. 144° (0.5 mm), n^{20}_D 1.4810, d_4^{20} 0.9454, MR_D 88.75; calc. 88.36.

Found %: C 77.22, 77.50; H 11.56, 11.42. M 294.92. $C_{19}H_{34}O_2$. Calculated %: C 77.49; H 11.64.

The p-menthan-3-yl Δ^1-p-menthen-8-yl acetal of acetaldehyde. A mixture of 50 g of α-terpineol and 75 g of vinyl p-menthan-3-yl ether was used for the synthesis. The catalyst was the normal one, but after its addition the reaction mixture was heated to 45°. As a result of the reaction, the temperature of the mixture rose spontaneously from 45 to 60°. The main fraction had:

B.p. 195-196° (1 mm), n^{20}_D 1.4729, d_4^{20} 0.9250, MR_D 101.30; calc. 101.31.

Found %: C 78.15, 77.94; H 11.97, 12.19. M 335.43. $C_{22}H_{40}O_2$. Calculated %: C 78.50; H 11.98. M 336.64.

In this synthesis, a by-product was obtained – the di-p-menthan-3-yl acetal of acetaldehyde.

B.p. 194° (2 mm), n^{20}_D 1.4704, d_4^{20} 0.9214, MR_D 102.46; calc. 102.68.

Found %: C 78.35, 78.32; H 12.39, 12.45. M 335.42. $C_{22}H_{42}O_2$ Calculated %: C 78.04; H 12.20. M 338.55.

The formation of the di-Δ^1-p-menthen-8-yl acetal of acetaldehyde as a by-product is theoretically possible, but it could not be obtained in pure form in consequence of the close boiling points of the by-product fractions. It must be mentioned that, in the synthesis of the p-menthan-3-yl Δ^1-p-menthen-8-yl acetal of acetaldehyde, all the by-product fractions had pleasant floral odors.

The composition of the new materials was confirmed by hydrolytic oximation. The content of the appropriate acetal varied from 97.5 to 98.5%.

All the acetals obtained dissolved well in alcohol, ether, benzene, and other organic solvents, but did not dissolve in water. They had pleasant floral odors. The acetals readily condensed with vinyl ethers.

SUMMARY

The ethyl Δ^1-p-menthen-8-yl, n-butyl Δ^1-p-menthen-8-yl, p-methylcyclohexyl Δ^1-p-menthen-8-yl, and p-menthan-3-yl Δ^1-p-menthen-8-yl acetals of acetaldehyde, which have pleasant floral odors have been synthesized.

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SYNTHESIS AND INVESTIGATION OF VINYL ETHERS OF SOME ALKYL- AND ARYL-SUBSTITUTED PHENOLS

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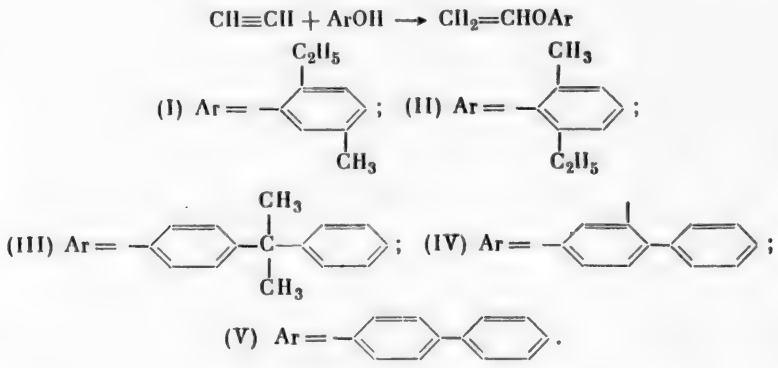
In order to study the chemical composition of the mixtures of phenols in the resin from the low-temperature carbonization of Cheremkhovo coals by means of the vinylation reaction [1, 2], it was important to obtain and investigate the vinyl ethers of some alkyl- and aryl-substituted phenols. Individual representatives of the vinyl ethers of alkyl-, dialkyl-, and aryl-substituted phenols subsequently found in the vinylated mixture of phenols of the primary resin from Cheremkhovo coals [2] had been obtained by us earlier [3, 4]. In addition to the problem of studying the composition of the mixture of phenols of the primary resin, the synthesis of the vinyl ethers of various substituted phenols is interesting also from the point of view of producing new monomers for polymerization and also for the production of new physiologically active substances [5].

In the present work, the vinyl ethers of 2-ethyl-5-methyl-, 2-methyl-6-ethyl-, p-cumyl-, and o- and p-phenylphenols were synthesized by the method of A. E. Favorskii and M. F. Shostakovskii [6] and their structure was demonstated.



The vinylation of the phenols mentioned was carried out under conditions similar to those for the synthesis of the vinyl ethers of the xylenols [3] and benzylphenols [4] obtained earlier. The vinyl ethers of 2-ethyl-5-methyl- and 2-methyl-6-ethyl phenols are colorless mobile liquids; the vinyl ethers of o-phenyl- and p-cumylphenols are viscous liquids with a glycerol-like consistency, a pale yellow color and an odor of fish oil, and the vinyl ether of p-phenylphenol was a crystalline substance with a green color. All the ethers are readily soluble in various organic solvents and are insoluble in water (table).

On comparing the constants of the ethers synthesized with the constants of the narrow fractions from the rectification of the mixture of vinyl ethers of the phenols from the low-temperature carbonization resin, it was conjectured that the 28th fraction, with b.p. 98.5-102.5° (20 mm), d_4^{20} 0.9453, $n^{20}D$ 1.5140, continued the vinyl ether of 5-methyl-2-ethylphenol. We hydrolyzed the vinyl ether of unknown structure from the 28th fraction and, from the phenol isolated on hydrolysis and monochloroacetic acid, we synthesized an arylglycolic acid [7], having m.p. 93-94°. The arylglycolic acid synthesized from 5-methyl-2-ethylphenol has the same melting point. The Raman spectra of the individual vinyl ether of 5-methyl-2-ethylphenol and the substance from the 28th fraction agreed with respect to the main lines. Consequently, the 28th fraction is, in fact, rich in the vinyl ether of 5-methyl-2-ethylphenol. The presence of the vinyl ether of p-phenylphenol in the mixture was shown earlier [8].

Constants of the Vinyl Aryl Ethers Synthesized

Compound No.	Vinyl ether	Boiling point (pressure in mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated	εM_D	Yield, (in %)	Found % C	Found % H	Empirical formula	Calculated % C	Calculated % H
I	2-Ethyl-5-methylphenol	73.5° (9)	0.9420	1.5130	51.77	50.57	1.20	79.0	81.30, 81.33	8.53, 8.56	$C_{11}H_{14}O$	81.48	8.64
II	2-Methyl-6-ethylphenol	103 (30)	0.9459	1.5075	50.95	50.57	0.38	66.7	81.12, 81.23	8.49, 8.51	$C_{11}H_{14}O$	81.48	8.64
III	p-Cumylphenol	149 (2)	1.0312	1.5710	75.70	74.68	1.20	72.00	85.88, 85.45	7.25, 7.21	$C_{17}H_{18}O$	85.60	7.61
IV	o-Phenylphenol	121.5 (5)	1.0651	1.5970	62.49	60.82	1.67	75.5	85.34, 85.39	5.92, 6.11	$C_{14}H_{12}O$	85.66	6.12
V	p-Phenylphenol	142.5 (5)*						78.1	85.49, 85.67	6.27, 6.09	$C_{14}H_{12}O$	85.66	6.12

* M.p. 39.5-40°.

We synthesized the initial alkyl- and aryl-substituted phenols by various methods known from the literature. 2-Ethyl-5-methyl- and 2-methyl-6-ethylphenols were synthesized from m- and o-cresols, respectively, through a number of stages (1) acetylation of the cresols [9], (2) rearrangement of the cresyl acetates obtained under the conditions of the Fries reaction into the isomeric ketocresols [10], and (3) hydrogenation by Clemensen's method of the 2-hydroxy-4-methyl- and 2-hydroxy-3-methylacetophenones to form 2-ethyl-5-methyl- and 2-methyl-6-ethylphenols [11].

o- and p-Phenylphenols are normal industrial products in the preparation of phenol by the alkali-fusion method [12]. There is also a whole series of patent specifications [13] on their production. The method of synthesis which we used [14] does not give good yields, but it was the most convenient under our conditions. The initial p-cumylphenol was obtained by the method of reference [15].

EXPERIMENTAL

2-Methyl-6-ethyl- and 2-ethyl-5-methylphenols. o-Cresyl acetate (VI), with b.p. 206-208° (736 mm), $n^{20}D$ 1.5019, was obtained from o-cresol [9]; m-cresyl acetate [9] (VII), with b.p. 212-213° (736 mm), $n^{20}D$ 1.5025, was obtained from m-cresol. To 50 g of (VI) heated to 130-140°, 40 g of $AlCl_3$ was added with stirring and the temperature was raised to 160° and maintained for 45 minutes. After cooling, the reaction mixture was treated with dilute hydrochloric acid and the reaction products were extracted with ether. Vacuum distillation yielded 13 g (26%) of 2-hydroxy-3-methylacetophenone (VIII) with b.p. 109-111° (13 mm), $n^{20}D$ 1.5430 (ortho isomer) and 5 g (10%) of 4-hydroxy-3-methylacetophenone (para isomer).

The rearrangement of (VII) was carried out under the same conditions; 56.2 g (56%) of 2-hydroxy-4-methylacetophenone (IX) with b.p. 91-93° (5 mm), $n^{20}D$ 1.5565 (ortho isomer) was obtained.

The hydrogenation of compound (VIII) and (IX) was carried out [11] in a round-bottomed flask with a reflux condenser in which were first placed 25 g of zinc dust, 2.5 g of mercuric chloride, 1.3 ml of hydrochloric acid, and 37.5 ml of water. The mixture was shaken for 5 minutes and the solution was decanted off. A mixture of 19 ml of water, 25 ml of concentrated hydrochloric acid, and 10 g of (VIII) or (IX) was added to the amalgamated zinc. The hydrogenation was carried out at the boil for 4 hours; after working up, from (VIII) 2-methyl-6-ethylphenol (X) (75%), b.p. 203-206° (736 mm), $n^{20}D$ 1.5310, was obtained and from (IX), 2-ethyl-5-methylphenol (XI) (60%) with m.p. 41-42°.

Vinyl ethers of 2-ethyl-5-methyl- and 2-methyl-6-ethylphenols (I) and (II). An autoclave was charged with 25 g of the phenol (X) or (XI), 3.75 g of KOH, and 7.5 ml of water, and acetylene was fed in under a pressure of 14 atm with a reaction temperature of 190-200°. The constants of the vinyl ethers (I) and (II) obtained are given in the table.

p-Cumylphenol. A mixture of 47.0 g of crystalline phenol and 34 g of dimethyl phenyl carbinol, obtained from bromo-

benzene, magnesium, and acetone [16], was placed in a three-necked flask with a mechanical stirrer, thermometer, and air condenser. Aluminum chloride (11.08 g) was added in small portions with cooling and stirring. After the addition of the whole amount of aluminum chloride, the reaction mixture was heated for 1 hour on the boiling water bath and then cooled and worked up in the usual way. Vacuum distillation yielded 57.2 g (70.5%) of p-cumylphenol with b.p. 186-187° (10 mm), m.p. 73-74°. Good cooling and the slow addition of the $AlCl_3$ have a favorable effect on the yield.

Vinyl ether of p-cumylphenol (III). A mixture of 50 g of p-cumylphenol, 12.2 g of KOH, and 24.4 ml of water was charged into an autoclave; the initial pressure of acetylene was 14 atm and the reaction temperature 210-220°. The acetylene was fed in two portions. The constants of the ether obtained (III) are given in the table.

Ethyl ether of p-cumylphenol. A mixture of 10 g of the vinyl ether of p-cumylphenol (III), 20 ml of ethanol, and 1.25 g of Raney nickel catalyst was charged into an autoclave to which hydrogen was supplied under a pressure of 36 atm. The hydrogenation was carried out 60° for 2 hours with constant rotation. A yield of 9.6 g (95.45%) of p-cumylphenol ethyl ether was obtained.

B.p. 196-197° (14 mm), d_4^{20} 1.0220, $n^{20}D$ 1.5613, MR_D 76.06; calc. 75.15.

Found %: C 85.10, 85.23; H 9.70, 9.56. $C_{17}H_{20}O$. Calculated %: C 84.95; H 9.87.

o- and p-Phenylphenols. To 375 ml of hydrochloric acid in a two-liter beaker with a mechanical stirrer was added 139.5 ml of freshly-distilled aniline. A solution of 120 g of $NaNO_2$ in 600 ml of water was added slowly to the cooled reaction mixture. The diazonium salt solution obtained was transferred to a two-liter round-bottomed flask with a reflux condenser, 200 g of phenol was added, and the mixture was heated until the evolution of nitrogen ceased. The lower oily layer was treated with a 5% solution of NaOH. The phenolates so extracted were decomposed with sulfuric acid and the liberated phenol layer was extracted with ether. The o-phenylphenol distillate (fraction boiling at 135-140° at 10 mm, 97 g) melted at 56-56.5° (from petroleum ether), which corresponds to data in the literature [17]. The p-phenylphenol (fraction boiling at 155-156° at 10 mm, 75 g) melted at 163.5-164° (from benzene).

Vinyl ethers of o- and p-phenylphenols (IV, V). The autoclave was charged with 17 g of o- or p-phenylphenol, 6.2 g of KOH, and 8.6 ml of water. The reaction temperature was 190-200°, and the time 1 hour. The constants of the ethers are given in the table.

SUMMARY

With the aim of studying the composition of the mixture of vinyl ethers of phenols from the resin from the low-temperature carbonization of Cheremkhovo coals, the new vinyl ethers of 2-ethyl-5-methyl-, 2-methyl-6-ethyl-, p-cumyl-, and o-phenyl- and p-phenylphenols have been synthesized individually. Conditions for the vinylation with yields of 70-78% of the phenols synthesized have been found. The presence of the vinyl ether of 2-ethyl-5-methylphenol in the mixture of vinyl ethers of the phenols of the primary resin from the low-temperature carbonization of Cheremkhovo coals has been shown on the basis of the experimental results.

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SYNTHESIS OF VINYL ETHERS OF o-, m-, and p-AMINOPHENOLS

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At the present time, aliphatic hydroxyamines can be successfully vinylated [1, 2]. However, there is no information in the literature on the vinylation of aminophenols. There is no doubt that an investigation of the reaction of acetylene with aromatic compounds in which two active groups, OH and NH_2, are present directly adjacent to a benzene ring is of particular interest for the production of vinyl monomers.

In the present work, we attempted to obtain vinyl ethers of aminophenols. Working with compressed acetylene, without a solvent, we have studied the influence of the amount of alkali, water, and the temperature on the yield of liquid reaction products. The dependence of the yield of vinyl ethers of the aminophenols on the reaction temperature is shown in Fig. 1. It can be seen from the shape of the curves that the vinylation of the aminophenols must be carried out within definite ranges of temperature for each isomer. The vinylation of the para isomer took place under the mildest conditions (170-180°). o-Aminophenol gave the highest yield of vinyl ether at 190°. m-Aminophenol, as the isomer with the highest thermal stability, was best vinylated at 210-220°. We used dilution of the reaction mixture with water as in the vinylation of phenol homologs [1, 3, 4]. Water in amount of 15-25% of the weight of the aminophenol favored a high yield of ether (Fig. 2). A further increase in the amount of water, and even two-fold dilution of the initial aminophenol with water, did not affect the yield of vinyl ether. However, a decrease in the amount of water or its complete absence led to pronounced resinification. In comparison with alkylphenols not containing amino groups, the aminophenols investigated were vinylated with a large amount of alkali in the reaction mixture. Thus, while the ordinary alkylphenols are best vinylated with 15-20% of KOH by weight of the phenol, the three isomeric aminophenols require 40% of KOH (Fig. 3). This amount corresponds to a molar ratio of the alkaline catalyst and the aminophenol. Hence, it must be assumed that the aminophenol reacts with acetylene after forming the potassium phenoxide.

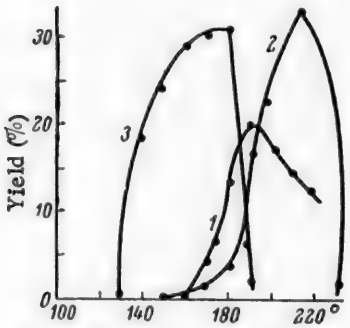

Fig. 1. Influence of the temperature on the yield of vinyl ethers in the presence of 25% of KOH and 50% of H_2O. 1) o-Aminophenol; 2) m-aminophenol; 3) p-aminophenol.

$$C_6H_4NH_2OH + KOH \longrightarrow C_6H_4NH_2OK + H_2O$$

$$C_6H_4NH_2OK + CH{\equiv}CH \xrightarrow{t^\circ,\ H_2O} C_6H_4NH_2OCH{=}CH_2 + KOH$$

The yield of vinyl ethers of the aminophenols amounted to 30-60% of the charge. The structure of the vinyl ethers of o-, m-, and p-aminophenols obtained was shown by the hydrogenation to the corresponding phenetidines. The reaction goes with a quantitative yield without contamination with by-products. The properties of the phenetidines obtained agreed with the literature data and partially supplemented them [5].

The aminophenol vinyl ethers investigated were hydrolyzed in the presence of a 2% solution of sulfuric acid at 90-100° with the liberation of acetaldehyde and polymerized under the influence of ionic catalysts.

EXPERIMENTAL

o-Aminophenol with m.p.174°, m-aminophenol with m.p. 123°, and p-aminophenol with m.p. 186° [6] were used.

Vinylation. A mixture of 20 g of the aminophenol, 1-10 g (5-50% of the weight of the phenol) of potassium hydroxide, and 3-25 g (15-125%) of water was heated in a rotating autoclave (capacity 0.5 liter) filled with acetylene under a pressure of 12-13 atm. The reaction mixture was held for 0.5 hr at the maximum temperatures indicated in Fig. 1. The working pressure in the autoclave reached 30-35 atm at 200°. In the best cases, about 10 atm were

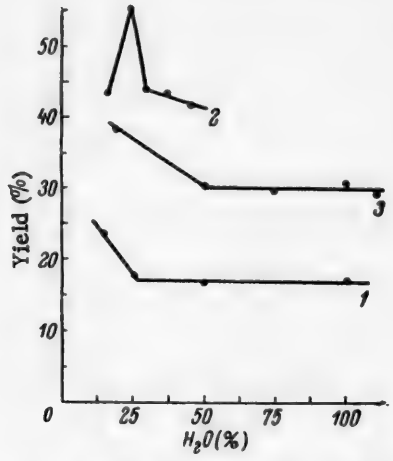

Fig. 2. Yield of vinyl ethers as a function of the amount of water. 1) o-Aminophenol; 2) m-aminophenol; 3) p-aminophenol.

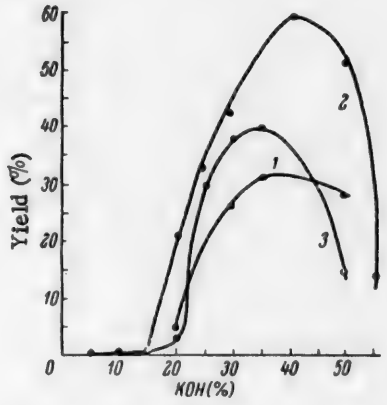

Fig. 3. Yield of vinyl ethers as a function of the amount of catalyst. 1) o-Aminophenol; 2) m-aminophenol; 3) p-aminophenol.

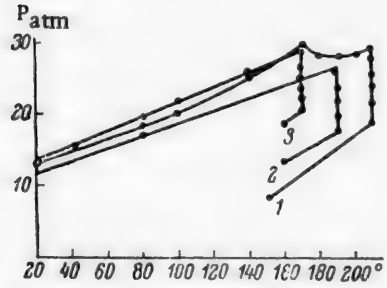

Fig. 4. Absorption of acetylene during vinylation. 1) m-Aminophenol; 2) o-aminophenol; 3) p-aminophenol.

adsorbed as a result of the reaction. The calculated amount of acetylene theoretically necessary for the production of an aminophenol vinyl ether is 6.7 atm. The absorption of acetylene under the optimum reaction conditions is shown in Fig. 4. The vinylation products, in the form of a brown or black viscous mass with a sharp smell of ammonia, were treated with benzene. Then the benzene and water were distilled off the benzene extracts. After this, high-boiling orange or reddish liquids and colorless crystals, which rapidly became yellow in air, were separated in a vacuum of 10-40 mm in a current of nitrogen. During distillation, the odor of indole was sometimes detected. These reaction products were not studied. The liquid fractions were dried over potash and repeatedly distilled in vacuum.

o-Aminophenol vinyl ether. The vacuum distillation of the vinylation products of o-aminophenol led to the isolation of 60.5 g of a yellow mass with b.p. 90° (10 mm) or 103° (17 mm), n_D 1.5700, which became red on standing. After drying with potash and subsequent vacuum distillation in a current of nitrogen, 50.8 g of colorless transparent liquid with the faint characteristic odor of vinyl ethers was obtained.

B.p. 66.5-68° (1-2 mm), 113° (24 mm), d_4^{20} 1.0677, n^{20}_D 1.5715, MR_D 41.56; calc.* 42.06.

Found %: C 71.06; H 6.71; N 10.29; O 11.94. M 135.3. C_8H_9ON. Calculated %: C 71.12; H 6.71; N 10.34; O 11.83. M 135.5.

m-Aminophenol vinyl ether. The liquid fractions having n_D 1.5825-1.5850 isolated by the vacuum distillation of the vinylation products of m-aminophenol were mixed. Then 73.3 g of the red-colored material was dried with potash and repeatedly purified by vacuum distillation. A yield of 63.6 g of the ether in the form of a colorless odorless clear liquid was obtained.

* In calculating the molecular refraction, the value of the atomic refraction for aromatic nitrogen was taken [7].

B.p. 92.5-93° (2 mm), 150.5° (40 mm), d_4^{20} 1.0759, $n^{20}D$ 1.5820, MR_D 41.90; calc.* 42.06.

Found %: C 71.15; H 6.91; N 10.35; O 11.50. C_8H_9ON. Calculated %: C 71.12; H 6.71; N 10.34; O 11.83.

p-Aminophenol vinyl ether. In the experiments on the vinylation of p-aminophenol, 60.1 g of a substance with b.p. 125-130° (14-17 mm), n_D 1.5720-1.5750 was obtained. This product was vacuum distilled, dried over calcined potash, and again distilled in a current of nitrogen. A yield of 52.0 g of the ether was obtained. It formed a colorless transparent oil which darkened on standing in air.

B.p. 118° (10 mm), 234-235.5° (736 mm), d_4^{20} 1.0759, $n^{20}D$ 1.5765, MR_D 41.54; calc.* 42.06.

Found %: C 70.98; H 6.72; N 10.37; O 11.93. M 134.5. C_8H_9ON. Calculated %: C 71.12; H 6.71; N 10.34; O 11.83. M 135.5.

o-Phenetidine. In a suitable vessel were placed 5.7 g of o-aminophenol vinyl ether and an alcoholic suspension of Raney nickel catalyst. Hydrogen was fed in from a gasometer. The reaction was carried out at room temperature with constant stirring until absorption of hydrogen ceased. In all, 1096.5 ml of gas (20°, 726 mm) was absorbed. The amount theoretically required for the hydrogenation of 5.7 g of C_8H_9ON is 1095 ml. On completion of the process, the catalyst was filtered off and the alcohol was removed on the water bath. The reaction product was distilled. A yield of 4.7 g of a colorless liquid was obtained.

B.p. 90-90.5° (3 mm), 224-226° (730 mm), d_4^{20} 1.0508, $n^{20}D$ 1.5557, MR_D 41.84; calc. 42.52. Literature data for o-phenetidine [5]: b.p. 228°.

m-Phenetidine. The hydrogenation of 5.1 g of m-aminophenol vinyl ether (n_D 1.5820) was carried out in a similar manner to that of the ortho isomer. In all, 980.3 ml of hydrogen (20°, 719 mm) was absorbed. Calculated for 5.1 g of C_8H_9ON, 978 ml. Fractionation yielded 4.8 g of material.

B.p. 247-248° (730 mm), d_4^{20} 1.0666, $n^{20}D$ 1.5660, MR_D 41.89; calc. 42.52.

Found %: C 70.03; H 8.08. $C_8H_{11}ON$. Calculated %: C 70.31; H 8.05.

The properties of the material obtained agreed with literature data for m-phenetidine [5]: b.p. 248°.

p-Phenetidine. The addition of hydrogen to 5.8 g of p-aminophenol vinyl ether was carried out in the presence of Raney nickel by the method described above. The absorption of hydrogen was 1112.0 ml (20°, 717 mm), calculated for 5.8 g of C_8H_9ON, 1117.0 ml. The main reaction product (4.0 g) was p-aminophenol ethyl ether.

B.p. 253° (730 mm), d_4^{20} 1.0525, $n^{20}D$ 1.5650, MR_D 42.40; calc. 42.52. Literature data [5]: b.p. 254.2-254.7°, $d_4^{15,9}$ 1.0652.

Polymerization. To 3 g of o-aminophenol vinyl ether was added 5-6 drops of stannic chloride in ether. After six months' the polymerizate remained liquid. In the presence of boron trifluoride etherate, the o-aminophenol vinyl ether was gradually converted into a carbonized solid mass with a multitude of lustrous black crystals. In polymerates of p-aminophenol vinyl ether under the influence of the same catalysts, a white crystalline precipitate appeared on the second day. Subsequently, the ether was converted into a solid orange and pale brown opaque resin.

SUMMARY

1. The applicability of the Favorskii – Shostakovskii method to the preparation of vinyl ethers of the aminophenols has been demonstrated.

2. The influence of the temperature, the catalyst and water on the reaction of the aminophenols with acetylene under pressure has been studied.

3. The vinyl ethers of o-, m-, and p-aminophenols have been synthesized and characterized for the first time.

4. The possibility of polymerizing the aminophenol vinyl ethers in the presence of cationic catalysts has been established.

5. o-, m-, and p-Phenetidines have been obtained by the hydrogenation of the aminophenol vinyl ethers.

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ORGANOSILICON COMPOUNDS WITH HYDROCARBON BRIDGES BETWEEN SILICON ATOMS

IV. THE PYROLYSIS OF α,ω-DISILALKANES

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Continuing the investigation of the properties of α,ω-disilalkanes [1-3], in the present work we have studied the pyrolysis of α,ω-disilalkanes of the type $R_3Si(CH_2)_nSiR_3$, where R = Cl, CH_3 and n = 1-4, at 600° in a continuous system.

The thermal stability of the α,ω-disilalkanes was determined from the amounts (1) of gaseous and volatile products formed (2) of heavy residues (with boiling points above that of the starting materials), and (3) the gases evolved.

As follows from the data of the table, the α,ω-hexamethyldisilalkanes investigated decompose in the following sequence of decreasing thermal stability.

$$\underset{(I)}{(CH_3)_3SiCH_2Si(CH_3)_3} \gg \underset{(II)}{(CH_3)_3Si(CH_2)_3Si(CH_3)_3} \geqslant \underset{(III)}{(CH_3)_3Si(CH_2)_2Si(CH_3)_3} > \underset{(IV)}{(CH_3)_3Si(CH_2)_4Si(CH_3)_3}$$

The stability of compounds (II-IV) changed inconsiderably with an increase in the length of the chain. It is interesting to note that the thermal stability in the pairs of compounds $(CH_3)_3SiCH_2CH_3 - (CH_3)_3SiCH_2CH_2Si(CH_3)_3$ and $(CH_3)_3SiCH_2CH_2CH_3 - (CH_3)_3SiCH_2CH_2CH_2Si(CH_3)_3$ (table) is approximately the same or even lower in the case of the monosilanes; while, from analogy with the hydrocarbons, a fall in the thermal stability of the silicohydrocarbons with an increase in the molecular weight might be expected. The high thermal stability of (I) in comparison with (II-IV) is probably due to the thermodynamic advantageousness of the structure $\equiv SiCH_2Si\equiv$.*

No alkyl monosilanes were found in the products of the pyrolysis of (I). This definitely shows the absence of any decomposition of the $\equiv SiCH_2Si\equiv$ fragment, and, at the same time, the composition of the pyrolysis gas (only CH_4 and H_2) indicates that in this compound the methyl groups connected to the silicon undergo conversion.

As a result of the pyrolysis of (III) the following are formed in the reaction mixture: $CH_2 = CHSi(CH_3)_3$, $(CH_3)_3SiH$, $(CH_3)_4Si$. From $Cl_3SiCH_2CH_2SiCl_3$ (V) a mixture of $CH_2 = CHSiCl_3$ (mainly) and $CH_3CH_2SiCl_3$, and also Cl_3SiH and $SiCl_4$, is obtained; and from $Cl_2(CH_3)SiCH_2CH_2Si(CH_3)Cl_2$ (VI) a mixture of $CH_2 = CHSi(CH_3)Cl_2$ (mainly) and $CH_3CH_2Si(CH_3)Cl_2$, and CH_3SiCl_2H and CH_3SiCl_3. The formation of the pyrolysis products indicated can easily be explained on the basis of the decomposition of the disilethane chain.

$$R_3SiCH_2CH_2SiR_3 \longrightarrow R_3Si\cdot + \cdot CH_2CH_2SiR_3.$$

* Apparently this fact explains the course of a series of reactions and rearrangements in which $\equiv SiCH_2Si\equiv$ structures are formed "unexpectedly." Thus, $\equiv SiCH_2Si\equiv$ structures are formed from $R_3Si - SiR_3$ (R is alkyl or chloroalkyl) under the influence of catalysts [4] or high temperatures [5]; $\equiv SiCH_2Si\equiv$ structures are also formed from methylsilyl chlorides or $Si(CH_3)_4$ under pyrolysis conditions [6] and on heating with catalysts [7].

Results of the pyrolysis of α,ω-Hexamethyldisilalkanes

Experiment No.	Formula of the material	Rate (in g-mole/hr)	Degree of pyrolysis*		
			A (%)	B(ml)	C (%)
1	$(CH_3)_3SiCH_2Si(CH_3)_3$	0.079	< 2	60	3.8
	The same	0.078	The same	60	4.0
2	$(CH_3)_3Si(CH_2)_2Si(CH_3)_3$	0.134	18.1	—	6.5
3	The same	0.079	29.5	303	7.9
4	$(CH_3)_3Si(CH_2)_3Si(CH_3)_3$	0.080	27.6	—	3.5
5	The same	0.079	29.2	234	4.2
6	$(CH_3)_3Si(CH_2)_4Si(CH_3)_3$	0.079	44.9	760	10.2
7	$(CH_3)_3SiCH_2CH_3$	0.139	38.8	—	7.2
8	$(CH_3)_3SiCH_2CH_2CH_3$	0.080	28.8	—	10.2
9	$(CH_3)_3SiCH_2CH=CH_2$	0.080	42.7	—	16.7
10					

* A is the weight % of gaseous and volatile substances calculated from the formula $\frac{M_1 - M_2}{M_1 - 1} \cdot 100$, where M_1 is the weight of the initial disilalkane and M_2 is the weight of the pyrolysis products of the disilalkane after distilling off the volatile products (monosilanes); the mechanical losses of the experiments were taken as 1 g. B is the volume of gases liberated on pyrolysis (at 20 ± 2°) in ml per 0.1 g-mole of disilalkane at the given rate, C is the percentage by weight of high-boiling substances (with b.p. > b.p. of the initial material) in the pyrolysis products.

The radicals formed undergo further conversions, for example:

$$R_3Si\cdot + \cdot CH_2CH_2SiR_3 \longrightarrow R_3SiH + CH_2{=}CHSiR_3;$$

$$2\cdot CH_2CH_2SiR_3 \longrightarrow CH_2{=}CHSiR_3 + CH_3CH_2SiR_3;\ \cdot CH_2CH_2SiR_3 \longrightarrow CH_2{=}CH_2 + HSiR_3$$

R = CH_3, Cl or combination of them.

The $SiCl_4$ from (V) may be formed from $HSiCl_3$ as a result of a secondary reaction [8], or, which is more probable, directly by conversion of the $Cl_3Si\cdot$ radicals.

If decomposition of the disilethane grouping also took place at the C − C bond, then the pyrolysis products from (V) should contain CH_3SiCl_3, and the pyrolysis products of (VI) should contain $(CH_3)_2SiCl_2$. However, the two methylchlorosilanes, which are quite stable to heat, were not found in the reaction products. For the 1,3-disilylpropane compounds, it is possible to envisage two additional schemes for the decomposition of the disilalkane group.

$$R_3SiCH_2CH_2CH_2SiR_3 \longrightarrow R_3Si\cdot + \cdot CH_2CH_2CH_2SiR_3$$

$$R_3SiCH_2CH_2CH_2SiR_3 \longrightarrow R_3SiCH_2\cdot + \cdot CH_2CH_2SiR_3$$

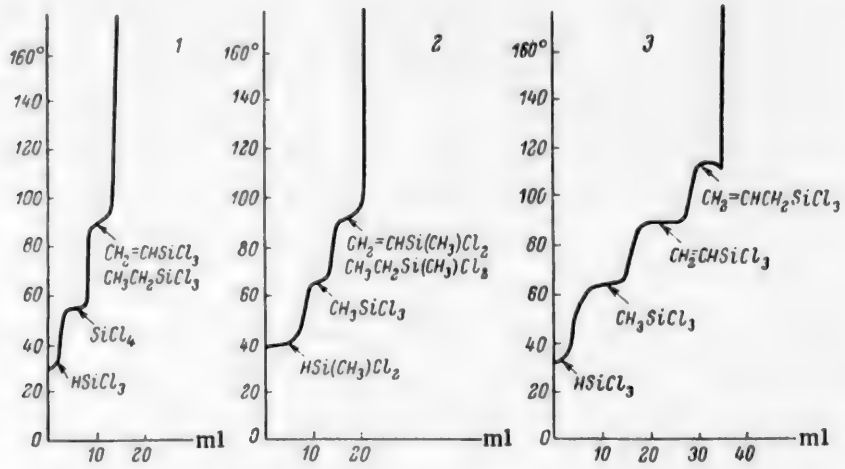
The $(CH_3)_3SiH$ formed in the pyrolysis of (II) and the Cl_3SiH and $CH_2 = CHCH_2SiCl_3$ formed in the pyrolysis of $Cl_3SiCH_2CH_2CH_2SiCl_3$ (VII) indicate the manner of the Si − C decomposition of the disilpropane chain. At the same time, the $CH_2 = CHSi(CH_3)_3$ isolated from the pyrolysis products of substance (II) and the Cl_3SiCH_3 and $CH_2 = CHSiCl_3$ isolated in the case of substance (VII) could be formed by a C − C rupture of the bridge group.

The $HSi(CH_3)_3$, $CH_2 = CHSi(CH_3)_3$, $CH_2 = CHCH_2Si(CH_3)_3$ and, probably, $CH_2 = CHCH_2CH_2Si(CH_3)_3$ found in the reaction products from (IV) permit the assumption that the disilbutane group in this case decomposes both through the Si − C and the C − C bonds.

Thus, under the action of high temperatures, the $\equiv Si(CH_2)_nSi\equiv$ chain ($n \geq 2$) decomposes both at the Si − C and the C − C bonds. It must be noted that under the action of metal halides [1-3] these disilalkanes decompose only at the Si − C bonds, while in the case of aluminum halides this decomposition is accompanied by redistribution of the Si − C bonds of the disilalkanes to form polymeric silicohydrocarbons with the simultaneous elimination of $Si(CH_3)_4$.

EXPERIMENTAL

The initial α,ω-disilalkanes were obtained by known methods: (I) [9], (II, III, V, VI) [10], (VII) [11], and (IV) [3]. The pyrolysis was carried out in an empty quartz tube (internal diameter 14 mm) placed in a catalysis furnace 600 mm long; the temperature of the furnace was 600 ± 5°. The disilalkanes were fed at a constant rate and the reaction products were collected in a receiver cooled to from −10 to −15°. The gaseous products were collected in a



Distillation curves of the pyrolysis products: 1) 1,2-Hexachlorodisilethane; 2) 1,2-dimethyltetrachlorodisilethane; 3) 1,3-hexachlorodisilpropane.

gasometer. In each experiment, about 50-100 g of α,ω-disilalkane was used. Before the beginning of the experiment, the system was purged with dry nitrogen, and after completion of an experiment the gasometer was disconnected and the system was again purged with nitrogen. The results of the experiments are given in the table and in the figure. The reaction mixtures were distilled in a column with 20 theoretical plates. The monosilane fractions – the pyrolysis products – were analyzed using infrared or Raman spectra and a comparison of the physical properties of the compounds obtained with those given in the literature.

No appreciable amount of monosilane derivatives was found in the products from substance (I) (experiment 2, table) under pyrolysis conditions. The gaseous reaction products consisted of 93.9% of H_2 and 6.1% of CH_4 (here and subsequently, the composition of the gaseous products is given in percent by volume).

Substance (III) (experiment 4, table) yielded 13.5%* of $CH_2 = CHSi(CH_3)_3$ with b.p. 54-55°, $n^{20}D$ 1.3890, d_4^{20} 0.6860. Literature data [13]: b.p. 55°, $n^{20}D$ 1.3902, d_4^{20} 0.6903. In addition, 10.5% of low-boiling products with b.p. 8-29°, consisting mainly of $(CH_3)_3SiH$ and $(CH_3)_4Si$ were obtained. The gaseous products contained (in %): 76.5 H_2, 7.2 CH_4, 1.5 C_2H_6, and 6.0 C_2H_4.

Substance (II) (experiment 6) yielded fractions with b.p. 16-25° (8.5%), consisting of $(CH_3)_3SiH$ and $Si(CH_3)_4$ and fractions with b.p. 25-28°, $n^{20}D$ 1.3596, d_4^{20} 0.6498 (7%), consisting of $Si(CH_3)_4$; literature data [12]: b.p. 26.5, $n^{20}D$ 1.3591, d_4^{20} 0.6480; and also 8.5% of $(CH_3)_3SiCH = CH_2$ with b.p. 54-56.5°, $n^{20}D$ 1.3900, d_4^{20} 0.6885. The gaseous products contained (in %): 88.6 H_2, 5.0 CH_4, 0.4 C_2H_6, 3.0 C_2H_4, and 0.8 C_3H_6.

Substance (IV) (experiment 7) yielded fractions with b.p. 0-53° containing $(CH_3)_3SiH$, $(CH_3)_4Si$, and unsaturated substances; 7% of $(CH_3)_3SiCH = CH_2$ with b.p. 54-57°, $n^{20}D$ 1.3882; 4.5% of $(CH_3)_3SiCH_2CH = CH_2$ with b.p. 86-87°, $n^{20}D$ 1.4085, d_4^{20} 0.7175; literature data [14]: b.p. 85°, $n^{25}D$ 1.4036, d_4^{25} 0.7158. The infrared spectrum of the fraction with b.p. 107-102° ($n^{20}D$ 1.4210, d_4^{20} 0.7532) showed frequencies characteristic for $(CH_3)_3SiCH_2CH = CH_2$. The gaseous products contained (in %): 24.3 H_2, 18.6 CH_4, 2.9 C_2H_6, 42.9 C_2H_4, and 4.2 C_3H_6.

Substance (V) (rate 0.084 g-mole/hr) yielded 2.5% of $HSiCl_3$ with b.p. 30-34°; 6% of $SiCl_4$ with b.p. 55-58°; and a fraction with b.p. 88-93°, $n^{20}D$ 1.4338, d_4^{20} 1.2718 (4.5%) – a mixture of $CH_2 = CHSiCl_3$ and $CH_3CH_2SiCl_3$ with

* The liquid products obtained in a reaction are given as percentages of the weight of the initial compounds.

a content of the latter of 20-30%. The remainder of the material, with b.p. > 180°, consisted practically completely of the initial substance (V) (after distillation, m.p. 24.5-26.5°); 82% of the initial substance (V) was recovered.

Substance (VI) (rate 0.087 g-mole/hr) yielded 5.0% of $HSi(CH_3)Cl_2$ with b.p. 39-44°; 4.0% of CH_3SiCl_3 with b.p. 63-67°, n^{20}_D 1.4100; and a fraction with b.p. 90-97°, n^{20}_D 1.4270, d_4^{20} 1.1040 (6%) – a mixture of $Cl_2(CH_3)SiCH = CH_2$ and $Cl_2(CH_3)SiCH_2CH_3$ with a content of the latter of 20-30%. The distillation residue with b.p. > 180° (84% of the weight of the initial compound) was methylated, 41 g of material being obtained from 70 g of the residue and CH_3MgCl (from 50 g of Mg): 1st fraction 142-150°, n^{20}_D 1.4204, d_4^{20} 0.7554, 3 g; 2nd fraction 150-151°, n^{20}_D 1.4200, d_4^{20} 0.7531, 28 g; 3rd fraction 151-153°, n^{20}_D 1.4227, d_4^{20} 0.7600, 10 g; residue, 4 g. The $(CH_3)_3SiCH_2CH_2Si(CH_3)_3$ obtained from the pure substance (VI) had the following constants: b.p. 150-152°, n^{20}_D 1.4205, d_4^{20} 0.7528. The Raman spectra of the 1st and 2nd fractions agreed completely with the Raman spectrum of pure $(CH_3)_3SiCH_2CH_2Si(CH_3)_3$; the 3rd fraction also consisted of hexamethyldisilethane with impurities giving weak lines at 398 and 537 cm^{-1} in the Raman spectrum. Thus, it has been established that neither dehydrogenation of the disilethane chain to ≡SiCH = = CHSi≡ nor isomerization into ≡SiCHSi≡, which are possible under pyrolysis conditions, take place appreciably under
|
CH_3

our conditions.

Substance (VII) (rate 0.084 g-mole/hr) yielded 0.5% of $HSiCl_3$ with b.p. 30-35°; 5.0% of CH_3SiCl_3 with b.p. 63-66°, n^{20}_D 1.4122, d_4^{20} 1.2824; and 6% of $CH_2 = CHSiCl_3$ with b.p. 88.5-90.5°, n^{20}_D 1.4355, d_4^{20} 1.2670; literature data [15]: b.p. 90°, n^{20}_D 1.436, d_4^{20} 1.28; no contamination with $Cl_3SiCH_2CH_3$ was found in this material according to the Raman spectrum. In addition, 1% of $Cl_3SiCH_2CH = CH_2$ with b.p. 114-115°, n^{20}_D 1.4449, d_4^{20} 1.2636, was obtained.

Found %: Cl 61.2, 60.8. $C_3H_5SiCl_3$. Calculated %: Cl 60.7.

Literature data [16]: b.p. 116.5°, n^{20}_D 1.4447, d_4^{20} 1.2224. The residue with b.p. > 180° was distilled; 81% of a substance with b.p. 109-112° (16 mm) was obtained; methylation of it with twice the calculated amount of CH_3MgCl yielded $(CH_3)_3SiCH_2CH_2CH_2Si(CH_3)_3$ with b.p. 169-171°, n^{20}_D 1.4210-1.4219, d_4^{20} 0.7600-0.7580; yield 80%. The data given in the literature [10] for this disilpropane are: b.p. 171.7°, n^{30}_D 1.4220, d_4^{20} 0.7560, and a similar Raman spectrum to that obtained.

In conclusion the authors express their thanks to E. Lubush and Yu. P. Egorov, who carried out the spectrum analysis.

SUMMARY

1. The pyrolysis of α,ω-hexamethyldisilalkanes at 600° in a continuous system has been studied under comparable conditions. The following sequence of thermal stabilities has been established:

$$(CH_3)_3SiCH_2Si(CH_3)_3 \geqslant (CH_3)_3Si(CH_2)_3Si(CH_3)_3 \geqslant (CH_3)_3Si(CH_2)_2Si(CH_3)_3 > > (CH_3)_3Si(CH_2)_4Si(CH_3)_3.$$

2. It has been established from analysis of the pyrolysis products that the compounds $R_3Si(CH_2)_nSiR_3$ (R = Cl, CH_3) decompose through the disilalkane group ≡$Si(CH_2)_nSi$≡, the decomposition proceeding through the Si – C bonds for n = 2, and through both Si – C and C – C bonds for n > 2.

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FERMENTATIVE SYNTHESIS OF OPTICALLY ACTIVE PEPTIDES FROM RACEMIC AMINOACIDS. II.

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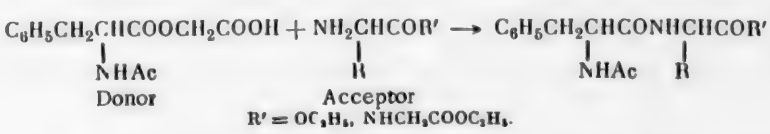
It has previously been shown that glycolic esters of benzoyl- and benzoxycarbonyl-DL-phenylalanine react with ethyl esters of DL-aminoacids and peptides in the presence of chymotrypsin with the formation of optically active peptides [1].



In the present work, the optimum reaction conditions have been studied and the behavior of the glycolic esters of acylated aliphatic aminoacids under the conditions of the fermentative synthesis of peptides has been elucidated; investigations have been continued into the spatial specificity of the reaction and the conditions for the isolation of the D-antipodes of the aminoacids have been worked out. Using the reaction of the glycolic ester of benzoyl-DL-phenylalanine with the ethyl ester of glycine as an example, the influence of various factors (the pH of the medium, the temperature, the ratio of the reactants) on the yield of reaction product has been ascertained. It was found that the optimum conditions for the synthesis of peptides are a pH of 8-8.5, a temperature of 20°, and a ratio of the donor (D) to acceptor (A) of 1 : 5. The results are shown in the figure. On carrying out the reaction under these conditions, the yield of the ethyl ester of benzoyl-L-phenylalanylglycine amounted to 70.6% (Table 1, experiment 6).*

In addition to the glycolic esters of the acylphenylalanine, the glycolic esters of acylated aliphatic aminoacids – hippuric acid, benzoyl-DL-alanine, benzoyl-DL-valine, benzoyl-DL-leucine, and benzoxycarbonyl-DL-leucine – were used as donors. The experiments were carried out under the optimum conditions found. The glycolic ester of hippuric acid reacts with the ethyl ester of glycine and the methyl ester of glycylleucine, but does not react with the ethyl ester of leucine (Table 1, experiment 1), which, however, readily reacts with the glycolic ester of benzoxycarbonylphenylalanine [1]. The glycolic esters of benzoyl-DL-alanine and benzoyl-DL-valine do not react with the ethyl esters of glycine, DL-leucine, and DL-leucylglycine (Table 1, experiments 2 and 3). The glycolic esters of benzoyl-DL-leucine and benzoxycarbonyl-DL-leucine, with the ethyl ester of glycine, form the corresponding ethyl esters of benzoyl-L-leucylglycine and benzoxycarbonyl-L-leucylglycine with yields of 30 and 13%. The latter, however, does not react with the methyl and ethyl esters of DL-leucine or the ethyl ester of DL-phenylalanine (Table 1, experiment 5). If the methyl ester of DL-leucine is used as the acceptor, the salt of benzoxycarbonyl-L-leucine and the methyl ester of leucine is produced. Thus, of the glycolic esters of the aliphatic aminoacids present in the composition of proteins, only the glycolic esters of acylglycines and acylleucines react as acceptors in the peptide synthesis, and then only with certain acceptors (see Table 1). In this connection it must be noted that attempts to obtain peptides from the ethyl ester of valine [2] and from O-benzoylvalyl-N-benzoylserine [3] under the action of chymotrypsin were also unsuccessful. Nevertheless, as special experiments have shown (see below), all the glycolic esters of acylated aminoacids investigated are hydrolyzed by chymotrypsin.

The results obtained permit the assumption that the reaction under investigation proceeds similarly to the protease, and not the esterase, reaction of chymotrypsin. The hydrolysis of esters of aminoacids by chymotrypsin

* The yield given is calculated on the L-antipode of the glycolic ester of the acylamino acid.

TABLE 1

Experiment No.	Donor – glycolic ester	Acceptor	Ferment used	Apparent changes in reaction solution	Yield of reaction product
1	Hippuric acid	a) Glycine ethyl ester b) Glycyl-DL-leucine methyl ester c) DL-leucylglycine ethyl ester	Crystalline chymotrypsin	None	a) Hippurylglycine ethyl ester (10%)* b) Hippurylleucine methyl ester (10%)
2	Benzoyl-DL-alanine	a) Glycine ethyl ester b) DL-leucine ethyl ester	–	None	–
3	Benzoyl-DL-valine	a) Glycine ethyl ester b) DL-leucine ethyl ester c) DL-leucylglycine ethyl ester	Crystalline chymotrypsin Amorphous ferment	None –	–
4	Benzoyl-DL-leucine	Glycine ethyl ester	Ditto	Precipitate	Benzoyl-L-leucylglycine ethyl ester (30%)*
5	BZC-DL-leucine	a) Glycine ethyl ester b) DL-leucine methyl ester c) DL-phenylalanine ethyl ester	Crystalline chymotrypsin	Precipitate Precipitate None	a) BZC-L-leucylglycine ethyl ester (13%)* b) Salt of BZC-L-leucine and leucine methyl ester
6	Benzoyl-DL-phenylalanine	Glycine ethyl ester	–	Precipitate	Benzoyl-L-phenylalanylglycine ethyl ester (70.6%)**
7	BZC-DL-phenylalanine	a) Glycine ethyl ester b) DL-alanine ethyl ester c) L-alanine ethyl ester d) D-alanine ethyl ester	Crystalline chymotrypsin	Precipitate – Precipitate Precipitate	a) BZC-L-phenylalanineglycine ethyl ester (60%)*** b) BZC-L-phenylalanylalanine ethyl ester (31%) c) Ditto (46%) d) BZC-L-phenylalanyl-D-alanine ethyl ester (8.9%)

* In an experiment with 0.2 g of the glycolic ester.
** In an experiment with 2 g of the glycolic ester.
*** In an experiment with 1 g of the glycolic ester.

TABLE 2. Alkaline Hydrolysis of the Glycolic Ester of Benzoxycarbonyl-DL-phenylalanine. Initial concentration $8.5 \cdot 10^{-5}$ mole/ml

Δt (min)	t (min)	pH	Percent hydrolysis after Δt min	Percent hydrolysis after t min
70	70	9.12	5.57	5.57
45	115	9.55	4.35	9.92
50	165	10	8.9	18.92
50	205	10.5	13.2	32.0
40	245	11	21.3	53.0
Alkaline hydrolysis of the glycolic ester of benzoxycarbonyl-DL-leucine				
50	50	9.05	3.57	3.57
30	80	9.5	3.4	6.97
30	110	10	4.27	11.24
30	140	10.5	7.34	18.58
20	160	11	6.87	25.45

does not greatly depend on the nature of the acid and alcohol residues of the substrate [4, 5]. However, the proteolytic action of chymotrypsin is more specific. Chymotrypsin hydrolyses peptide bonds formed by aromatic aminoacids, tryptophan, methionine, and threonine [6]. Preliminary experiments carried out with the glycolic esters of tryptophan, methionine, and threonine confirm this situation. Under the action of chymotrypsin, they all react with esters of aminoacids, forming the corresponding optically active peptide esters.

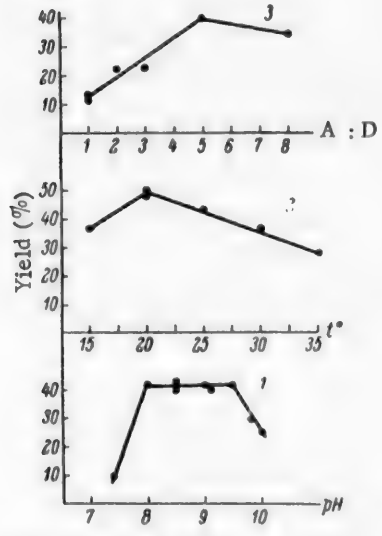


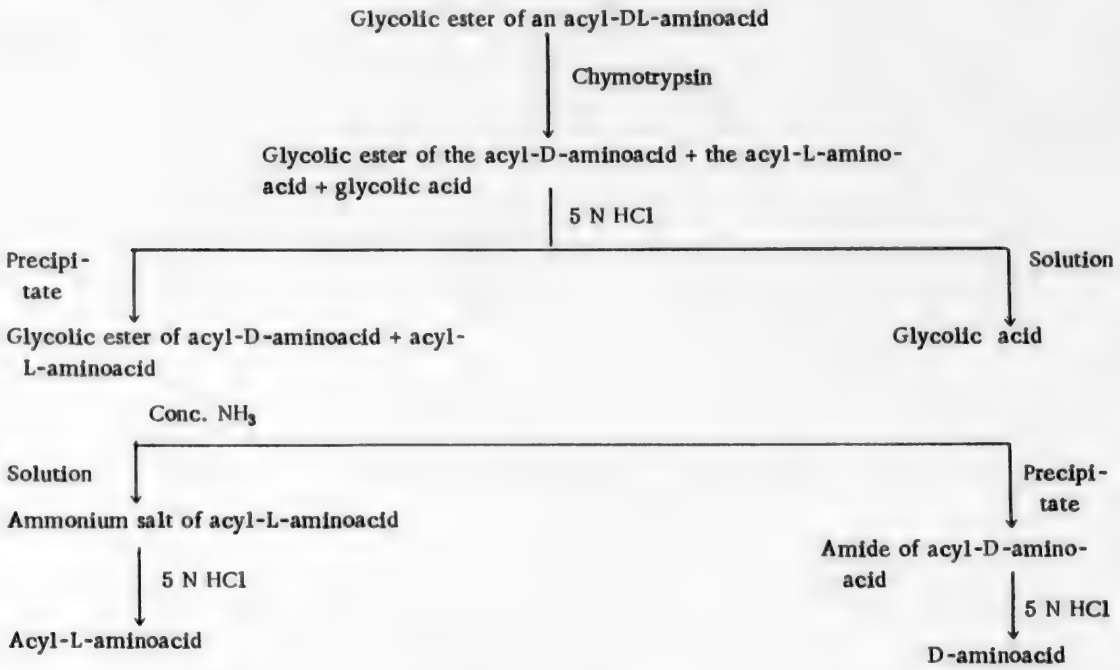
Figure. Yield of ethyl ester of benzoyl-L-phenylalanylglycine as a function of: 1) pH (30°, A : D = 5); 2) the temperature (pH 8, A : D = = 5); 3) the A : D ratio (pH 8, 30°).

In the previous work, the ethyl esters of glycine, DL-leucine, DL-leucylglycine, DL-phenylalanylglycine, and glycylglycine were used as acceptors. The stereospecificity of the synthesis was shown by the fact that the use of esters of DL-aminoacids and L-aminoacids as acceptors led to the same L,L-peptides. In the present investigation, experiments were carried out on the reaction of the glycolic ester of bzc* -DL-phenylalanine with the ethyl esters of DL- and L- and D-alanine. In agreement with the results obtained earlier in experiments with the ethyl esters of DL - and L-alanine, the ethyl ester of benzoxycarbonyl-L-phenylalanyl-L-alanine was obtained with a yield of 46%. However, the glycolic ester of benzoxycarbonyl-L-phenylalanine in the absence of L-alanine ethyl ester reacted likewise with D-alanine ethyl ester with the formation of the ethyl ester of benzoxycarbonyl-L-phenylalanyl-D-alanine (yield 6.9%). Thus, the specificity of chymotrypsin with respect to the spatial configuration of the acceptor in the reaction studied is not absolute. To test the stereospecificity of chymotrypsin with respect to a donor, the ethyl ester of benzoxycarbonyl-L-phenylalanylglycine, obtained from the glycolic ester of benzoxycarbonyl-DL-phenylalanine and glycine ethyl ester in the presence of chymotrypsin, was subjected to complete hydrolysis and the specific rotation of the phenylalanine formed was determined.

It was found to be −6.9° (c 3.5, 4 N HCl), $[\alpha]_D$ for phenylalanine is −7.07° (c 3.5, 4 N HCl). Hence it may be concluded that only the L-component of the donor takes part in the fermentative synthesis.

* Benzoxycarbonyl.

The glycolic esters of acylated aminoacids, like the ethyl and methyl esters of aminoacids and the N-acyl-O-peptides of serine and threonine, are hydrolyzed by chymotrypsin. Hydrolysis with the latter takes place considerably faster than with alkalis (see Tables 2 and 3). Hydrolysis with chymotrypsin depends little on the nature of the alcohol and acid residues, but only the L-antipode of a compound undergoes hydrolysis. The comparative fermentative hydrolysis of the glycolic esters of benzoxycarbonyl-L- and benzoxycarbon-D-phenylalanine was carried out (experiments 6 and 7, Table 3) and it was found that the latter is not split by chymotrypsin. The glycolic esters of acylated aminoacids, like the O-peptides of serine and threonine, react very readily with ammonia, forming the corresponding amides. Using these two reactions – stereospecific hydrolysis and aminolysis – the separation of benzoyl-DL-phenylalanine and benzoxycarbonyl-DL-leucine into their optical antipodes was carried out. The scheme of separation is given below.



This reaction was also used for the separation of the amide of benzoxycarbonyl-D-phenylalanine from the mother liquors remaining after the production of the ethyl ester of benzoxycarbonyl-L-phenylalanylglycine. The yield of benzoyl-D-phenylalanine amide was 84% (optical purity 87%), of benzoxycarbonyl-D-leucine amide 68% (optical purity 97%), and benzoxycarbonyl-D-phenylalanine 80% (optical purity 80%).

EXPERIMENTAL

I. Fermentative Synthesis of Optically Active Peptides from Glycolic Esters of Racemic Acylamino Acids*

1. Determination of the optimum reaction conditions. A solution of 0.438 g of glycine ethyl ester hydrochloride in 3.15 ml of 1 N NaOH and 2 ml of a phosphate buffer with pH 8 was added to a solution of 0.2124 g of the glycolic ester of benzoyl-DL-phenylalanine in 0.7 ml of alcohol and 0.63 ml of 1 N NaOH. The solution was brought to pH 8, 5 ml of "amorphous ferment"** was added, and the mixture was stirred in a thermostat at 30°. After 15 minutes a voluminous precipitate began to form, and after 2 hours it was filtered off, washed with small portions of 0.15 N sodium carbonate solution and water, and dried at 80-100°. The yield of the ethyl ester of benzoyl-L-phenylalanylglycine was 0.0443 g (41.2 % calculated on the L-antipode), m.p. 148-149°; literature data: 148-149° [3, 10]. Experiments on the determination of the dependence of the yield of the L-peptide ester on the pH of the medium, the temperature, the ratio of the donor and acceptor, and the amount of ferment were carried out in a similar manner. The results obtained are given in the figure.

* Synthesis of the glycolic esters of acetylated aminoacids, see [1, 8, 9].

** Ground pancreas was repeatedly washed with alcohol and then extracted at 0° with a saturated solution of common salt and the "amorphous" ferment was precipitated from the solution with absolute acetone.

TABLE 3. Hydrolysis of Glycolic Esters of Acylated Aminoacids by Chymotrypsin

Experiment No.	Glycolic ester	Ferment	Substrate (mole/ml) 10^{-5}	Ferment (mg/ml)	Temperature	pH	Percent hydrolysis after 30 min.	Maximum hydrolysis
1	Benzoyl-DL-phenylalanine	Crystalline	6.69	$22 \cdot 10^{-2}$	22°	8	29.5	46.7
		Amorphous	5.56	$45 \cdot 10^{-2}$	20	8.1	27.8	—
			8.7	—	20	8	0.25	
2	Benzoyl-DL-valine	Amorphous	8.55	$70 \cdot 10^{-5}$	20	8.1	6.5	38.86
			7.47	—	20	8.05	0.1	
3	Benzoyl-DL-valine	Amorphous	10.9	$69 \cdot 10^{-2}$	20	8.1	5.5	48.3
			9.82	—	20	8.05	0.1	
4	Hippuric acid	Amorphous	8.4	$77 \cdot 10^{-5}$	20	7.95	40	—
5	Benzoxycarbonyl-DL-phenylalanine	Amorphous	21	$64 \cdot 10^{-2}$	20	8.2	11.2	50.4
			4.87	—	20	8.1	1.2	
6	Benzoxycarbonyl-L-phenylalanine	Crystalline	8.77	$9.8 \cdot 10^{-2}$	23	8.1	15.5	—
			8.77	—	23	8.1	1.3	
7	Benzoxycarbonyl-D-phenylalanine	Crystalline	8.77	$38.6 \cdot 10^{-2}$	23	8.1	1.1	—
8	Benzoxycarbonyl-DL-leucine	Crystalline	4.7	$73 \cdot 10^{-2}$	22	8.1	19	35
			3.9	—	22	8.2	1.1	

2. Ethyl ester of benzoyl-L-phenylalanylglycine (under the optimum conditions found). A solution of 4.186 g of glycine ethyl ester hydrochloride in 30.6 ml of 1 N NaOH and 10 ml of phosphate buffer (pH 7.8) was added to a solution of 2 g of the glycolic ester of benzoyl-DL-phenylalanine in 5 ml of alcohol and 6.11 ml of 1 N NaOH, and the pH of the solution was brought to 8.15. Then 20 mg of amorphous ferment was added and the mixture was left for 2 hours at 20°. The precipitate which separated was washed with 0.15 N sodium carbonate solution and water, and dried. The yield was 0.706 g (70.6%, calculated on the L-antipode), m.p. 147.5-149°.

3. Ethyl ester of benzoxycarbonyl-L-leucylglycine. The experiment was carried out with 0.2 g of the glycolic ester of benzoxycarbonyl-DL-leucine and 0.34 g of glycine ethyl ester hydrochloride without the addition of alcohol. One and one half hours after the addition of the ferment (5 mg of "amorphous" ferment or 0.5-1 mg of crystalline chymotrypsin), needle-like crystals of the ester precipitated. Yield 14 mg (13%), m.p. 106-107°,* $[\alpha]^{18}_D$ −25.2° (c 1, alcohol).

4. Ethyl ester of benzoyl-L-leucylglycine. The experiment was carried out with 0.4 g of the glycolic ester of benzoyl-DL-leucine and 1.2 g of glycine ethyl ester hydrochloride (without the addition of alcohol). Thirty minutes after the addition of the chymotrypsin, needle-like crystals of the ethyl ester of benzoyl-L-leucyglycine separated out. The yield was 57 mg (30%), m.p. 154.5-156° (from water); $[\alpha]^{18}_D$ −38.84° (c 2, alcohol).

Found %: N 8.93, 9.02. $C_{17}H_{24}O_4N_2$. Calculated %: N 8.75.

5. Hippurylglycine ethyl ester. To a mixture of 0.2 g of the glycolic ester of hippuric acid, 1.05 g of glycine ethyl ester hydrochloride, and 0.5 ml of alcohol, 1 N NaOH was slowly added with constant stirring to pH 8, and 2 ml of phosphate buffer. The mixture was divided into two equal portions and to one of them was added 1 mg of crystalline chymotrypsin. On standing for a day at 20°, neither of the solutions underwent any visible change. The solutions

* Literature data: m.p. 104-105°, $[\alpha]^{20}_D$ −26.4° (c 5, alcohol) [11]; m.p. 103-104°, $[\alpha]^{20}_D$ −25.6° (c 5, alcohol) [12]; m.p. 104-105° [13]; m.p. 99-102°, $[\alpha]^{20}_D$ −27.2° (c 5, alcohol) [14].

were evaporated in vacuum and extracted with chloroform, and the chloroform extracts were washed with 0.5 N sodium carbonate, water, and 1 N HCl, and evaporated. In the experiment with the ferment, hippurylglycine ethyl ester was obtained. Yield 5 mg (10%), m.p. 115-116°; according to data in the literature, m.p. 116-117° [15].

The other experiments on the reaction of the glycolic esters of acylated aminoacids with the ethyl esters of aminoacids and dipeptides in the presence of chymotrypsin were carried out similarly (Table 1).

6. Ethyl ester of benzoxycarbonyl-L-phenylalanyl-L-alanine. a) To 0.21 g of the glycolic ester of benzoxycarbonyl-DL-phenylalanine and 0.7 g of DL-alanine ethyl ether hydrochloride in 1 ml of alcohol, 1 N NaOH was added with stirring to pH 8. Then a solution of 3 mg of crystalline chymotrypsin in 2 ml of phosphate buffer was added. The experiment was carried out at 20°. After 20 minutes, the separation of a needle-like precipitate of the ethyl ester began. It was separated off and washed with 0.15 N sodium carbonate solution, water, and 1 N HCl. Yield 37 mg (31%, calculated on the L-antipode), m.p. 121.5° (after recrystallization from alcohol), $[\alpha]^{18}_D$ −19.68° (c 2, alcohol).

b) A similar result was obtained on using "amorphous" ferment.

c) On carrying out the experiment with 0.2 g of the glycolic ester of benzoxycarbonyl-L-phenylalanine and 0.28 g of L-alanine ethyl ester hydrochloride ($[\alpha]^{18}_D$ +8.53°, c 2, water) under the conditions described, we obtained 51 mg of the ethyl ester of benzoxycarbonyl-L-phenylalanyl-L-alanine − 46%, calculated on the L-antipode. m.p. 122.5-123°, $[\alpha]^{18}_D$ −22.2° (c 1, alcohol). All three preparations give no depression of the melting point when mixed.

Found %: C 66.14, 66.30; H 6.71, 6.64; N 7.20, 7.22. $C_{22}H_{26}O_5N_2$. Calculated %: C 66.33; H 6.53; N 7.03.

7. Ethyl ester of benzoxycarbonyl-L-phenylalanyl-D-alanine. The experiment was carried out in a similar manner to that described with 0.23 g of the glycolic ester of benzoxycarbonyl-DL-phenylalanine, 0.35 mg of D-alanine ethyl ester hydrochloride ($[\alpha]^{18}_D$ −8.3°, c 2, water) and 3 mg of crystalline chymotrypsin. Forty-five minutes after the addition of the ferment, the separation of a precipitate of the ester commenced. The yield was 18 mg (8.9%), m.p. 127.5-128° (from aqueous alcohol), $[\alpha]^{18}_D$ +58.06° (c 1.5, alcohol).

Found %: C 66.27, 66.09; H 6.67, 6.66. $C_{22}H_{26}O_5N_2$. Calculated %: C 66.33; H 6.53.

II. Fermentative Hydrolysis of the Glycolic Esters of Acylated DL Aminoacids

1. The glycolic ester of the acylated DL aminoacid was dissolved in the minimum amount of alcohol and an equimolecular amount of alkali and 0.1 N NaOH to pH 8-8.3 and a solution of 3-5 mg of the ferment in 2 ml of phosphate buffer (pH 8.1) were added. After definite intervals of time, the pH of the solution was determined potentiometrically and it was restored to its original value by the addition of 0.1 N NaOH. Two blank experiments were carried out simultaneously. One with the substrate without the addition of the ferment and the other with the ferment without the addition of the substrate. The results of the hydrolysis are given in Table 3.

2. Separation of acylaminoacids into their optical antipodes. a) Separation of the glycolic ester of benzoyl-DL-phenylalanine. One gram of the ester was hydrolyzed with crystalline chymotrypsin for 1 hour and then the solution was acidified with 5 N HCl. The precipitate which separated was washed with water and treated with a concentrated aqueous solution of ammonia. After 12 hours at 20°, a precipitate of benzoyl-D-phenylalanine amide separated and was washed with water. The yield was 84%. The mother liquors, containing the ammonium salt of benzoyl-L-phenylalanine were left for 24 hours at 0°. The small amount of benzoyl-D-phenylalanine amide which separated was removed and the solution was acidified with 5 N HCl, upon which benzoyl-L-phenylalanine separated; yield 0.42 g (95%), m.p. 140°, $[\alpha]_D$ + 17° (c 6.025, N KOH); according to data in the literature: m.p. 144° $[\alpha]_D$ +17.1° (c 6.025, N KOH) [7]. The benzoyl-D-phenylalanine amide was hydrolyzed for 10 hours with 5 N HCl, the solution was evaporated in the vacuum desiccator over alkali; water was added, the benzoic acid was filtered off, and the filtrate was treated with ammonia. From 0.35 g of benzoyl-D-phenylalanine amide we obtained 0.12 g of D-phenylalanine, $[\alpha]^{20}_D$ +30.5° (c 1, H_2O); according to the data in the literature, $[\alpha]^{20}_D$ +35° (c 2, H_2O) [16].

3. Separation of the glycolic ester of benzoxycarbonyl-DL-leucine into its antipodes. One gram of the ester was hydrolyzed with crystalline chymotrypsin and treated as described above. A yield of 0.4 g of benzoxycarbonyl-L-leucine was obtained in the form of a clear transparent oil, hydrogenation of which in alcoholic acetic acid solution over Pd black yielded L-leucine. The yield was 0.24 g (96%), $[\alpha]^{20}_D$ −13.5° (c 4, 20% HCl). According to data in the literature, $[\alpha]^{20}_D$ −15.6° (c 4, 20% HCl) [17]. The yield of benzoxycarbonyl-D-leucine amide was 0.278 g (68%), m.p. 122-124°. The compound has not been described in the literature. Hydrogenation of 75 mg of

the amide in alcoholic acetic acid solution over Pd black yielded 50 mg (94%) of the acetate of D-leucine amide. M.p. 127-128°, $[\alpha]^{21}_D$ –8.96° (c 1, H_2O); according to data in the literature, m.p. 128-129°, $[\alpha]^{20}_D$ –9.2 (c 1, H_2O] [18].

4. Isolation of the amide of benzoxycarbonyl-D-phenylalanine and preparation of D-phenylalanine amide hydrochloride. The ethyl ester of benzoxycarbonyl-L-phenylalanylglycine was obtained from 1.8 g of the glycolic ester of benzoxycarbonyl-DL-phenylalanine and 3 g of glycine ethyl ester hydrochloride in the presence of crystalline chymotrypsin and was separated from the solution. A further 2 mg of the ferment was added to the mother liquors and they were left at pH 8 and 20° for 4 hours. The amide of benzoxycarbonyl-D-phenylalanine was isolated in the same way as the amides of benzoyl-D-phenylalanine and benzoxycarbonyl-D-leucine. The yield of amide was 0.6 g, m.p. 162°; according to data in the literature: m.p. 167° [16]. The amide of benzoxycarbonyl-D-phenylalanine was hydrolyzed in aqueous hydrochloric acid solution over Pd/C and the amide of DL-phenylalanine was obtained. Yield 0.25 g, $[\alpha]^{18}_D$ –16.55° (c 2, H_2O); according to data in the literature, $[\alpha]^{18}_D$ –20.4° (c 2, H_2O) [19].

SUMMARY

1. The optimum conditions for the fermentative synthesis of L-peptides from glycolic esters of acyl-DL-phenylalanines have been determined.

2. The alkaline and fermentative hydrolysis of the glycolic esters of acylated aminoacids has been studied.

3. It has been shown that the fermentative hydrolysis of the glycolic esters of acylaminoacids can be used for the separation of acyl-DL-aminoacids into their optical antipodes.

4. Using the synthesis of the ethyl ester of benzoxycarbonyl-L-phenylalanyl-D-alanine as an example, it has been shown that the specificity of chymotrypsin with respect to the configuration of the aminoacid of the acceptor is not absolute.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

SYNTHESIS OF P – N AMINOACID (PEPTIDE) DERIVATIVES OF ADENYLIC ACID AND INVESTIGATION OF THEIR PROPERTIES

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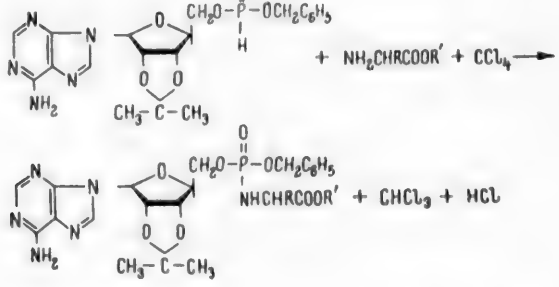
In science, more and more facts are always being gathered which indicate the presence in natural objects of nuclein – protein compounds in which the bond between the nucleotides and the peptides are apparently phosphoric amide (P – N) bonds. Porter and Dounce [1] were the first to investigate the alkaline hydrolyzates of RNA from the pancreas and liver of the rabbit, and also yeast RNA, in detail, and they found nucleotides in them to which they gave quantitative characteristics. In the formation of the so-called simple nucleotidopeptides, the nucleotides of the acid-soluble fractions may take part. Thus, Bergwist [2] isolated a peptidocytidylate from the acid-soluble fraction of polyporus sguamosus in which the nucleotide and the peptide were linked to one another by a covalent bond. Free guanylic, adenylic, uridylic, and cytidylic acids or their residues in the polynucleotides take part in the formation of simple nucleotidopeptides or nucleotidoaminoacids [3]. Simple compounds of nucleotide diphosphates with peptides have been found [4], some of them possessing fermentative activity [5]. Apparently, compounds with a phosphoric amide bond are extremely widespread in nature, if, for example, one takes into consideration the investigations of Perlmann [6], from whose experiments it follows that in α-casein about 40% of the phosphoserine is present in the form of a compound in which the bond between the aminoacid and the phosphoric acid is a phosphoric amide bond.

However, the chemistry of P – N aminoacid or peptide derivatives of nucleotides has not been studied. Conclusions on the structure and properties of natural P–N compounds of this type are made on the basis of analogy from the properties of the simple derivatives of amides of esters of phosphoric acid.

We undertook the task of working out methods for the synthesis of P – N aminoacid (peptide) derivatives of nucleotides and studying some of the chemical properties of these compounds. For the synthesis of these compounds it proved possible to use the reaction for preparing amides of nucleotides [7], using esters of aminoacids in the reaction instead of NH_3 or amines. From 2',3'-isopropylideneadenosine-5'-benzyl phosphite and esters of aminoacids or peptides, we succeeded in obtaining the corresponding esters of 2',3'-isopropylideneadenosine-5'-(benzyl)-phosphinyl-aminoacids (-peptides) in CCl_4 with yields amounting generally to 50-60%, by the scheme



The reaction proceeds at room temperature and is completed after 10-14 hours. In the case of lysine, its ε-amino group must be benzoxycarbonylated and when using glutaminic acid, both carboxyl groups were esterified.

TABLE 1. Esters of N-[2',3'-Isopropylideneadenosine-5'-(benzyl)-phosphinyl]-aminoacids

Name of the aminoacid residue	Yield, %	Analysis	Melting point	R_f in the system		ε at 260 mμ	Characteristic frequency (μ)
				1	3		
Glycine methyl ether	52	Found %: N 13.62; P 4.76. $C_{23}H_{29}O_8N_6P \cdot 3H_2O$. Calculated %: N 13.95; P 5.14	60-63° (With decomp.)	–	0.91	11500 in C_2H_5OH	11.48
Phenylalanine methyl ester	65	Found %: C 56.71; H 5.99; N 12.9; P 4.50. $C_{30}H_{35}O_8N_6P$. Calculated %: C 56.20; H 5.50; N 13.20; P 4.90	79-81 (With decomp.)	0.87	0.91	11100 in C_2H_5OH	–
Phenylalanine ethyl ester	62.5	Found %: C 53.45; H 5.96; N 11.76; P 4.20. $C_{31}H_{37}O_8N_6P \cdot 3H_2O$. Calculated %: C 53.14; H 6.14; N 11.90; P 4.30	88-90 (With decomp.)	0.93	0.91	13250 in C_2H_5OH	11.59
Leucine methyl ester	44	Found %: N 12.2; P 4.3. $C_{27}H_{37}O_8N_6P \cdot 3H_2O$. Calculated %: N 12.8; P 4.7	68-72 (With decomp.)	– –	0.93	9800 in C_2H_5OH	11.56
N_ε-Benzoxycarbonyl lysine	54	Found %: C 55.76; H 6.23; P 4.02; N 12.35. $C_{35}H_{44}O_{10}N_7P$. Calculated %: C 55.75; H 5.84; P 4.12; N 13.0	50-55 (With decomp.)	0.85	0.90	11200 in C_2H_5OH	–
Glutamic acid diethyl ester	62	Found %: C 52.55; H 6.25; P 4.01. $C_{29}H_{39}O_{10}N_6P$. Calculated %: C 52.6; H 5.8; P 4.7	70-76 (With decomp.)	0.86	0.89	9940 in C_2H_5OH	–

A list of the compounds obtained is shown in Table 1. With respect to absorption in the UV region, the compounds had λ_{max} 260 mμ, which is characteristic for the adenine nucleus, and in the IR region they had a frequency at 11.48-11.59 μ which is characteristic for a P – N bond in the P-diesters of the phosphoaminoacids [8]. The compounds are comparatively difficult to hydrolyze with acid and alkali (37°), hydrolysis in acid medium, however, always proceeding more readily. On hydrolysis, the corresponding aminoacids are formed. It must be noted that derivatives of an adenosine-5'-(benzyl)-phosphinylaminoacid are distinguished by a far greater stability to hydrolysis in alkaline media than the derivatives of an adenosine-2'-(benzyl)-phosphinylaminoacid. But, there, this is connected with the ease of formation of the 2,3-cyclophosphate [9].

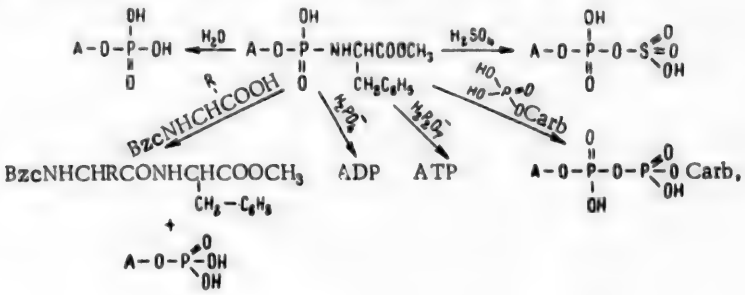
Passage from the adenosine-5'-(benzyl)-phosphinyl derivative to the adenosine-5'-phosphinyl derivative was readily achieved by hydrogenation over Pd black for 2 hours in the presence of triethylamine. The triethylammonium salt of the ester of the N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-aminoacid formed was far more stable on storage than the ester itself. The triethylammonium salt of the N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-aminoacid was readily hydrolyzed by acid (1 N HCl, 37°, 80 minutes) and with more difficulty by alkali (boiling with 1 N NaOH). On hydrolysis of the acid, the esters of the corresponding aminoacid and of adenylic acid were formed. The bond between the adenylic acid and the aminoacids is not split by phosphomonoesterase (pH 5.6), chymotrypsin (pH 7.88), or ribonuclease (pH 7.88).

We were interested in the question of the chemical activity of the compounds obtained with respect to the P – N bond and the possibility of passing from them to ADP, ATP, coferments, peptides, and other physiologically important compounds. Goldschmidt and Krauss [10] have shown that the amides of diesters of phosphoric acid, on reaction with carboxylic acids, scarcely form amides of the carboxylic acids, while monoesters of amides of phosphoric acids readily react with the formation of the amides of the carboxylic acids. On the other hand, Todd has proposed a method for the phosphorylation of nucleotides which consists in the action of phosphoric acid on the protonated amide of a nucleoside phosphate with the splitting out of an amide and the formation of a nucleoside pyrophosphate [11]. All this gave us the basis for supposing that the P – N bond in the compounds which we synthesized is fairly labile, and we were able to look forward to success in experiments on the action on our compounds of aminoacids, ortho- and pyrophosphoric acids, phosphocarbohydrates, and other compounds.

It was found that if the methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine was boiled in dioxane solution with bzc-aminoacids (glycine, valine, tyrosine), then, as was shown by chromatographic analysis, the corresponding dipeptides are formed. Peptide formation does not take place if the adenosine-5'-(benzyl)-phosphinyl derivative is used in place of the adenosine-5'-phosphinyl derivative.

The triethylammonium salt of the methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine reacts with a mixture of phosphoric and pyrophosphoric acids forming ADP and ATP. With H_2SO_4 (oleum) in pyridine, adenosine phosphosulfate is formed.

It was found to be possible to pass readily from the P – N aminoacid derivatives of adenylic acid to the coferment systems. When the triethylammonium salt of the methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine reacted with the tributylammonium salt of ribose-5'-phosphate in pyridine at room temperature for 2 days, 2',3'-isopropylideneadenosine-5'-diphosphoribose was formed. The reaction with glucose-6-phosphate under similar conditions led to the formation of 2',3'-isopropylideneadenosine-5'-diphosphoglucose. The general scheme of the chemical conversion can be represented in the following way.



where A is isopropylideneadenosine and Carb denotes ribose or glucose. The structure of the 2',3'-isopropylideneadenosine-5'-diphosphoribose was established by investigating the products of its hydrolysis in an acid medium. Adenosine, AMP, ADP, and ribose were isolated.

Thus, P – N aminoacid derivatives of adenylic acids posses high reactivity. From these compounds it is possible to obtain high-energy polyphosphates and coferments, and their aminoacid residues may be transferred to aminoacids and peptides, taking part in the peptide synthesis.

EXPERIMENTAL

The systems used in the chromatographic investigations were: system 1: n-butyl alcohol saturated with water; system 2: isoamyl alcohol saturated with a solution of Na_2HPO_4 and 5% Na_2HPO_4 solution saturated with isoamyl alcohol (1 : 2); system 3: n-butyl alcohol – water – acetic acid (4 : 5 : 1); system 4: n-butyl alcohol – water – acetic acid (5 : 3 : 2); system 5: n-butyl alcohol – water – acetic acid (4 : 1 : 1); system 6: isopropyl alcohol and 1 % $(NH_4)_2SO_4$ solution (2 : 1); system 7: 96% C_2H_5OH and 0.5 M ammonia – acetate buffer (pH 3.5) (5 : 2).

The methyl ester of N-[2',3'-isopropylideneadenosine-5'-(benzyl)-phosphinyl]-phenylalanine. A solution of 1.2 g (7 mole) of freshly prepared phenylalanine methyl ester in 30 ml of absolute CCl_4 was added to a solution of 1 g (2.1 mole) of anhydrous 2',3'-isopropylideneadenosine-5'-benzyl phosphite in 100 ml of absolute CCl_4. The reaction mixture was allowed to stand for 12 hours at room temperature. The solvent was evaporated off in vacuum at a temperature not above 40° and the oil remaining was dissolved in chloroform. The chloroformic solution was washed successively with water, dilute HCl solution, water, saturated $NaHCO_3$ solution, and water again, and dried over $MgSO_4$. The chloroform was evaporated off in vacuum and the oil remaining was dissolved in a small amount of absolute benzene and poured into absolute petroleum ether. A white amorphous precipitate deposited which was separated by decantation and dried in a vacuum desiccator over P_2O_5. It was purified by reprecipitation. Yield 0.9 g (65%). M.p. 79-81° (with decomp.). R_f 0.87 in system 1, 0.91 in system 3.

Absorption in the infrared: λ_{max} 260 mμ, ε 11.100 (in 95% C_2H_5OH).

Found %: C 56.75, 56.71; H 6.05, 5.99; N 12.9, 12.7; P 4.24, 4.50. $C_{30}H_{35}O_8N_6P$. Calculated %: C 56.20; H 5.50; N 13.20; P 4.90.

The compound is slowly hydrolyzed by 1 N acid and 1 N alkali at 37°. It is stable on storage. The other esters listed in Table 1 were obtained in a similar manner.

The compounds were hydrolyzed with acid and alkali, hydrolysis with acid going more intensively. A solution of 5 mg of the ethyl ester of N-[2',3'-isopropylideneadenosine-5'-(benzyl)-phosphinyl]-phenylalanine in 2 ml of 0.1 N H_2SO_4 was boiled for 30 minutes. By paper chromatography, the hydrolyzate was found to contain phenylalanine (R_f 0.72 in system 4) and a compound absorbing in the UV with λ_{max} 258-260 mμ and having R_f 0.47 in the same system, and none of the initial compound. A similar effect was observed on boiling the compound with 2 N NaOH for 30 minutes. In a similar way, on acid and alkaline hydrolysis of the methyl ester of N-[2',3'-isopropylideneadenosine-5'-(benzyl)-phosphinyl]-glycine, glycine (R_f 0.37 in system 4) was found, and on the hydrolysis of the methyl ester of N-[2',3'-isopropylideneadenosine-5'-(benzyl)-phosphinyl]-leucine, the formation of leucine was shown.

Methyl ester of N-[2',3'-isopropylideneadenosine-5'-(benzyl)-phosphinyl]-phenylalanylglycine. This was obtained in similar manner to the preceding compound from 2',3'-isopropylideneidenosine-5'-benzyl phosphite and the methyl ester of phenylalanylglycine. Yield 45%. M.p. 60-65° (with decomp.). R_f 0.83 (system 1) and 0.90 (system 3). Absorption in the UV: λ_{max} 260 mμ, ε 5900 (in C_2H_5OH).

Found %: C 54.54, 54.71; H 5.67, 5.73; N 13.25, 13.28; P 4.49, 4.36. $C_{32}H_{38}O_9N_7P$. Calculated %: C 55.25; H 5.47; N 14.1; P 4.46.

Triethylammonium salt of the methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine. A solution was made of 0.5 g of the methyl ester of N-[2',3'-isopropylideneadenosine-5'-(benzyl)-phosphinyl]-phenylalanine in 30 ml of 96% C_2H_5OH. To the solution was added 0.3 ml of absolute tirethylamine and hydrogenation was carried out over Pd black for 2 hours at room temperature. After completion of the reaction, the catalyst was filtered off and the solvent was evaporated in vacuum. The residual oil was dissolved in a few ml of absolute chloroform. The chloroform solution was poured into absolute petroleum ether. The white amorphous precipitate was separated by decantation. It was purified by reprecipitation. It was dried in a vacuum desiccator at room temperature over P_2O_5. Yield 0.4 g (78%). M.p. 85-90° (with decomp.). R_f 0.49 (system 1), 0.65 (system 2), 0.71 (system 3). Absorption in the UV in methyl alcohol: λ_{max} 260 mμ, ε 10570.

Found %: C 51.85, 51.79; H 6.48, 6.52; N 14.3, 14.42; P 4.80, 4.98. $C_{29}H_{44}O_8N_7P \cdot 3H_2O$. Calculated %: C 52.1; H 6.9; N 14.7; P 4.65.

The compound is fairly stable, but on protracted storage under ordinary conditions it slowly decomposes with the formation of phenylalanine methyl ester.

On chromatographing a hydrolyzate of the compound (1 N HCl, 37°, 60 minutes), the following were found: in system 1: phenylalanine methyl ester (R_f 0.69); in system 3, adenylic acid (R_f 0.77), and phenylalanine methyl ester (R_f 0.90). However, if the hydrolysis was carried out in 1 N NaOH under the same conditions, N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine having R_f 0.20 (in system 1) and 0.63 (in system 3) was formed. On boiling the compound with 1 N NaOH for 1 hour, adenosine and phenylalanine were found.

In order to evaluate the rate of hydrolysis quantitatively, the method of determining the aminoacid formed as a result of splitting the P – N bond was used. To a solution of 10 mg of the substance under investigation in 1-2 drops of anhydrous alcohol was added 1 ml of standardized hydrochloric acid solution (or caustic soda solution, if alkaline hydrolysis was being studied). The mixture was placed in a thermostat (37°) for definite intervals of time. The solution was neutralized and, first 1 ml of citrate buffer (pH 5) was added and then 1 ml of a solution of ninhydrin in alcohol (20 mg/ml) and, finally, 1 ml of alcohol. The mixture was heated for 20 minutes on the boiling water bath, transferred to a measuring flask, and diluted to 25 ml with 50% alcohol. After 15-60 min, the optical density of the solution was determined using a PEK-M photoelectric colorimeter. The measured values of the optical densities were compared with a calibration curve obtained by measuring the optical densities of a series of standard solutions of the appropriate aminoacid ester in alcohol. The results of the measurements are given in Table 2.

Fermentative hydrolysis. To a solution of 50 mg of the triethylammonium salt of the methyl ether of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine in a few drops of methanol, 2 ml of 1 N NaOH was added and the mixture was allowed to stand for 15 minutes in a thermostat at 37°. The solution was neutralized to pH 7 and divided into five portions. Citrate buffer, pH 5.6, and phosphomonoesterase were added to one of the portions, phosphate buffer of pH 7.88 and chymotrypsin to a second portion, and the same buffer and ribonuclease to a third portion. The last two portions were used as blanks. The tubes were left at room temperature for 2 hours, and then the solutions were chromatographed. Only the initial substance (R_f 0.2 in system 1) was found in all the portions. No degradation products of the compound investigated were found.

The methyl ester of N-(2',3'-isopropylideadenosine-5'-phosphinyl)-phenylalanine was obtained from 0.05 g of the methyl ester of N-[2',3'-isopropylideadenosine-5'-(benzyl)-phosphinyl]-phenylalanine by reduction over PdO in 50% methyl alcohol at room temperature for 30 minutes. The isolation of the product was carried out in a similar way to that used in the preceding case. Yield 0.029 g (67%). M.p. 116-118° (with decomp.). Absorption in the UV: λ_{max} 260 mμ (in C_2H_5OH). R_f 0.50 (in system 1).

Found %: C 48.91; H 5.78; N 15.48. $C_{23}H_{29}O_8N_6P \cdot 3H_2O$. Calculated %: C 48.90; H 5.51; N 15.90.

The substance is insufficiently stable. On storage for a few days it decomposes with the formation of new compounds having R_f 0.06 and 0.12 in system 1.

Reaction of the methyl ester of N-(2',3'-isopropylidenadenosine-5'-phosphinyl)-phenylalanine with bzc-aminoacids. To a solution of 23 mg of the freshly-prepared methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine in 50 ml of absolute alcohol was added 46 mg of bzc-glycine. The mixture was boiled for 2 hours. The precipitate which separated was filtered off. The filtrate was evaporated to dryness in vacuum and the residue was dissolved in 50 ml of chloroform and washed with 0.1 N HCl and 0.1 N NaOH. Then the solution was again evaporated in vacuum, and the residue was dissolved in 50 ml of 50% alcohol and subjected to hydrogenolysis over a Pd catalyst. The catalyst was separated by centrifuging, and the centrifugate was evaporated to a volume of 1-2 ml and chromatographed in system 1. The methyl ester of glycylphenylalanine (R_f 0.42), agreeing with a standard sample was found on the chromatogram.

The reaction with bzc-valine was carried out under similar conditions. On chromatography in system 1, a spot with R_f 0.69, corresponding to a reference spot of the methyl ester of valylphenylalanine was found.

On carrying out the reaction with the methyl ester of N-bzc-tyrosine, a chromatogram using system 5 gave a spot of the methyl ester of tyrosylphenylalanine (R_f 0.65), agreeing with a standard sample.

The methyl ester of N-[2',3'-isopropylideneadenosine-5'-(benzyl)-phosphinyl]-phenylalanine did not react with bzc-aminoacids under similar conditions.

TABLE 2. Course of the Hydrolysis of the Triethylammonium Salt of the Methyl Ester of N-(2',3'-Isopropylidenoadenosine-5'-phosphinyl)-phenylalanine in Acid Media

Acid	Temperature	Percent hydrolysis of the P – N bond			
		time (in minutes)			
		10	30	50	80
1 N HCl	37°	32	50	73	87
0.1 N HCl	37°	11	20	26	30

Reaction of the triethylammonium salt of the methyl ester of N-(2',3'-isopropylidenoadenosine-5'-phosphinyl)-phenylalanine with phosphoric and pyrophosphoric acids. Commerical orthophosphoric acid (d 1.67) was evaporated in vacuum at 180°. A mixture of phosphoric and pyrophosphoric acid was obtained. Anhydrous tributylamine was added to this mixture. The reaction mixture was gently heated in a vacuum. A mixture of the tributylammonium salts of ortho- and pyrophosphoric acids was obtained.

An equivalent amount of HCl in absolute dioxane was added to a solution of 15 mg ($2 \cdot 10^{-5}$ mole) of the triethylammonium salt of the methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine in 1 ml of absolute dioxane. The triethylamine hydrochloride which separated as a precipitate was filtered off. To the filtrate was added 37 ml of the tributylammonium phosphate and pyrophosphate in 2 ml of absolute dioxane. The reaction mixture was left at room temperature for 3 hours, protected from atmospheric moisture. Then the reaction mixture was transferred to paper and subjected to electrophoresis in 0.075 M ammonia-acetate buffer (pH 3,5) for 2 hours at 15 V/cm. AMP, ADP, and ATP were found in the reaction mixture in the form of intense spots, visible in ultraviolet light, which agreed completely with reference samples. Calculation of the yield of reaction products, from the measurements of the optical densities of the eluates at 260 mμ, gave 39% for ADP and 27% for ATP.

Chromatography of the mixture in system 6 gave spots with R_f 0.19, 0.33, 0.52, and 0.69. The spot with R_f 0.19 corresponded to the reference spot for ATP. The spot with R_f 0.33 corresponded to the reference spot for ADP, and the spot with R_f 0.52 to the reference spot for AMP.

Reaction of the methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine with sulfuric acid. To 450 mg of cooled 40% oleum, were added 4 ml of anhydrous pyridine and 20 mg of the freshly-prepared methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine in 1 ml of pyridine. The mixture was left for 90 hours at room temperature. The precipitate was filtered off, and the filtrate was evaporated to a small volume and subjected to electrophoresis in an acetate buffer, (pH 4.8; 5 V/cm) for 6.5 hours. Besides the initial substance, an intense spot absorbing in the ultraviolet (λ_{max} 260 mμ) and corresponding to a reference sample of ADP was found on the electrophorogram. Sulfur was found in an eluate of the spot. The yield of sulfur derivative, determined from the optical density of the eluates at 260 mμ, was 61%.

Reaction of the triethylammonium salt of the methyl ether of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine with carbohydrate phosphates. a) With ribose-5-phosphate. A solution of the tributylammonium salt of ribose-5-phosphate (52 mg or $1.2 \cdot 10^{-4}$ mole) in 1.5 ml of dry pyridine was added to a solution of 20 mg ($3.1 \cdot \cdot 10^{-5}$ mole) of the triethylammonium salt of the methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphinyl)-phenylalanine in 1 ml of anhydrous pyridine. The reaction mixture was allowed to stand at room temperature for 70 days, protected from atmospheric moisture, and was then separated by paper chromatography in system 7. The reaction product was readily separated from the initial substances, giving a spot with R_f 0.50. The yield of the substance amounted to 25% (from the optical density). The substance was eluted and hydrolyzed with 0.01 N HCl at 100° for 10 minutes. The hydrolyzate was chromatographed in three different systems: Found: in system 6: R_f 0.32 (ADP), 0.54 (AMP), 0.62 (ribose), 0.79 (adenosine); in system 7: R_f 0.32 (ADP), 0.54 (AMP), 0.71 (ribose), 0.74 (adenosine); in system 3: R_f 0.23 (adenosine), 0.24 (ribose). The eluate of the ADP spot was subjected to electrophoresis in a borate buffer (pH 8.28; 7 V/cm) for 2 hours. The single spot was shown up by ultraviolet light on the electrophorogram; it migrated in the same way as a reference sample of ADP.

b) With glucose-6-phosphate. An equivalent amount of HCl in absolute dioxane was added to 20 mg ($3.1 \cdot 10^{-5}$ mole) of the triethylammonium salt of the methyl ester of N-(2',3'-isopropylideneadenosine-5'-phosphenyl)-phenylalanine dissolved in 1 ml of absolute dioxane. The precipitate was filtered off. To the filtrate was added 1.6 ml of a solution of the tributylammonium salt of glucose-6-phosphate ($1.2 \cdot 10^{-2}$ mole) in dry pyridine. The reaction mixture was allowed to stand at room temperature. The reaction mixture was separated by chromatography in system 7. It had R_f 0.49. Yield 37%.

To determine the structure and composition of the reaction product, it was hydrolyzed with 0.01 N HCl at 100° for 10 minutes and chromatographed. The following results were obtained: in system 6, spots were found with R_f: 0.22 (ADP), 0.41 (AMP), 0.54 (glucose), 0.74 (adenosine); in system 7, R_f: 0.41 (ADP), 0.57 (AMP), 0.64 (glucose); in system 3, R_f: 0.14 (glucose), 0.37 (adenosine). The eluate of the ADP spot was subjected to electrophoresis as described above. A spot travelling at the same rate as a reference sample was found on the electrophorogram.

SUMMARY

1. A method for the synthesis of P – N aminoacid (peptide) derivatives of adenylic acid has been developed which is based on the reaction of aminoacid (or peptide) esters with derivatives of adenosine-5'-benzyl phosphite in CCl_4.

2. The physical and chemical properties of the P – N aminoacid derivatives of adenylic acid have been studied. It has been shown that the reaction of these compounds with a mixture of H_3PO_4 and $H_2P_2O_7$ leads to the formation of ADP and ATP. The reaction with phosphocarbohydrates (phosphoribose, phosphoglucose) leads to the formation of adenosinediphosphocarbohydrates. The reaction of the P – N aminoacid derivatives of adenylic acid with bzc-amino-acids leads to the formation of dipeptides.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

SYNTHESIS OF 2,3-QUINUCLIDINEDICARBOXYLIC ACID

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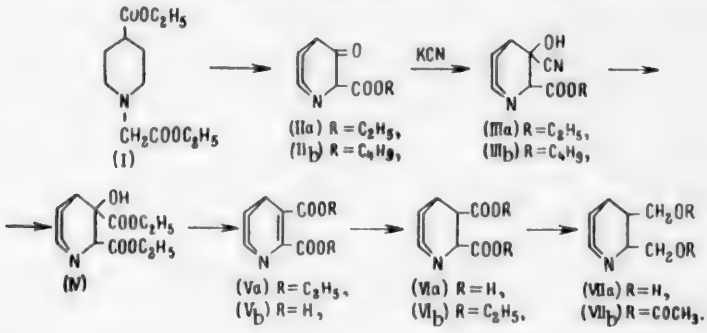
The quinuclidinecarboxylic acids can serve as the starting compounds for the synthesis of various substituted quinuclidine derivatives. The preparation of the three possible monocarboxylic acids of quinuclidine is described in the literature [1-3], and from them the synthesis of a large number of monosubstituted derivatives of the given bicyclic compound.

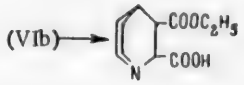
The dicarboxylic acids of quinuclidine are new compounds. Their synthesis represents definite interest.

In this paper we describe the synthesis of 2,3-quinuclidinedicarboxylic acid by the following scheme:



The starting compounds in the given synthesis are the ethyl and butyl esters of 3-oxo-2-quinuclidinecarboxylic acid (IIa, b). Ester (IIa) is formed by the cyclization of 1-carbethoxymethyl-4-carbethoxypiperidine (I) in the presence of potassium ethylate [4]. The use of potassium butylate as the condensing agent leads to the formation of ester (IIb). Reaction of the (II) compounds with potassium cyanide yields the ethyl (butyl) ester of 3-hydroxy-3-cyano-2-quinuclidinecarboxylic acid (IIIa, b), which when heated with a mixture of hydrochloric and acetic acids is converted to 3-hydroxy-2,3-quinuclidinedicarboxylic acid; the latter was converted directly to the corresponding diethyl ester (IV). Here, together with ester (IV), we isolated 3-quinuclidinone. The latter was formed by the decarboxylation of 3-oxo-2-quinuclidinecarboxylic acid, which, apparently, was formed by the decomposition of the α-hydroxy acid. Diester (IV) was dehydrated by treatment with thionyl chloride. The thus obtained diethyl ester of Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid (Va) was hydrolyzed with hydrochloric acid to Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid (Vb). The reduction of acid (Vb) in the presence of platinum gave 2,3-quinuclidinedicarboxylic acid (VIa). The saturated acid (VIa) forms a hydrochloride that is stable in aqueous solution, whereas the hydrochloride of acid (Vb) is easily hydrolyzed under these conditions. From diacid (VIa) we obtained the diethyl ester (VIb), which, by using aluminum lithium hydride, was converted to 2,3-bis(hydroxymethyl)quinuclidine (VIIa).

When the properties of the diethyl ester of 2,3-quinuclidinedicarboxylic acid (VIb) were studied it was found that on standing in water solution the compound is hydrolyzed with ease to yield the acid ester.



As we had previously shown, a similar transformation is characteristic for the ethyl ester of 3-carbethoxymethyl-2-quinuclidinecarboxylic acid [5]. In the latter case it is the carbethoxyl group in the 2-position that is hydrolyzed,

and the resulting acid ester has the structure of 3-carbethoxymethyl-2-quinuclidinecarboxylic acid. A comparison of the properties of the indicated esters gives reason to believe that in the diethyl ester of 2,3-quinuclidinedicarboxylic acid it is also the carbethoxyl group in the 2-position that undergoes hydrolysis, and the acid ester formed in the hydrolysis has the structure of 3-carbethoxy-2-quinuclidinecarboxylic acid (VIII).

EXPERIMENTAL

Butyl ester of 3-oxo-2-quinuclidinecarboxylic acid (IIb). Into a 2-liter flask, fitted with a stirrer, reflux condenser and a Dean and Stark trap, were charged 69.2 g of KOH, 1000 ml of n-butyl alcohol and 100 ml of toluene. The mixture was heated at the boil until the separation of water ceased, and then it was evaporated in vacuo to dryness. The solid residue was treated with 200 ml of anhydrous toluene, the mixture was heated to the boil, and then, with stirring, a solution of 120 g of 1-carbethoxymethyl-4-carbethoxypiperidine in 300 ml of toluene was added in 1 hour. The reaction mass was heated under reflux for 5 hr. After cooling, the toluene was decanted, and the residual viscous mass, being the potassium salt of the enol form of the butyl ester of 3-oxo-2-quinuclidinecarboxylic acid, was washed with toluene and then treated with 740 ml of 10% acetic acid. The acetic acid solution was neutralized with 170.2 g of potassium carbonate and the resulting oil was extracted with chloroform. The chloroform extract was dried, the solvent was distilled off, and the residue was vacuum-distilled. B.p. 137° (0.6 mm). The compound was obtained as a colorless, fairly viscous oil. It is readily soluble in water, alcohol, and chloroform. It crystallizes on standing. M.p. 88°. Yield 48 g (43.5%).

Found %: N 6.11, 6.66. $C_{12}H_{19}O_3N$. Calculated %: N 6.25.

Hydrochloride: colorless crystals, soluble in water and in alcohol, and insoluble in ether. M.p. 163°.

Butyl ester of 3-hydroxy-3-cyano-2-quinuclidinecarboxylic acid (IIIb). A solution of 5.1 g of potassium cyanide in 15 ml of water was added at 5°, with vigorous stirring, in 20 min, to a solution of 18.3 g of the hydrochloride of the butyl ester of 3-oxo-2-quinuclidinecarboxylic acid in 30 ml of water. After 1.5 hr the obtained precipitate was filtered, washed with water, and dried. We obtained 12 g (68.5%) of the butyl ester of 3-hydroxy-3-cyano-2-quinuclidinecarboxylic acid as colorless crystals, readily soluble in alcohol. M.p. 107°.

Found %: C 61.66; H 7.76; N 11.21. $C_{13}H_{20}O_3N_2$. Calculated %: C 61.89; H 7.95; N 11.12.

Ethyl ester of 3-hydroxy-3-cyano-2-quinuclidinecarboxylic acid (IIIa). A solution of 7.4 g of potassium cyanide in 15 ml of water was added in 15 min, at 5°, to a solution of 26.55 g of the hydrochloride of the ethyl ester of 3-oxo-2-quinuclidinecarboxylic acid [4] in 40 ml of water. The obtained precipitate was filtered, washed with water, and dried. Yield 18.5 g (73%). Colorless crystals, readily soluble in chloroform and alcohol, difficultly soluble in dioxane, and insoluble in water. M.p. 124-125° (from dioxane).

Found %: C 58.79; H 7.09; N 12.6. $C_{11}H_{16}O_3N_2$. Calculated %: C 58.92; H 7.15; N 12.5.

Diethyl ester of 3-hydroxy-2,3-quinuclidinedicarboxylic acid (IV). a) A mixture of 49 g of the ethyl ester of 3-hydroxy-3-cyano-2-quinuclidinecarboxylic acid, 1000 ml of glacial acetic acid and 500 ml of conc. hydrochloric acid was refluxed for 25 hr. At the end of this time the solution was evaporated, and the residue was dried by treating it 3 times with benzene, with removal of the benzene each time by vacuum-distillation. After this the residue was esterified by refluxing it twice with 500 ml of a 10% alcoholic solution of hydrogen chloride. The reaction mass was then evaporated, the residue was dissolved in 100 ml of water, followed by the addition of 100 ml of 50% potassium carbonate solution, and the whole was extracted with chloroform. The chloroform solution was dried over potassium carbonate, the solvent was distilled off, and the residue was vacuum-distilled. The first product to distill was 3-quinuclidinone (7.3 g), which sublimes at 18 mm and a bath temperature of 100-120°. This product was identified as the picrate. The next to distill was the diethyl ester of 3-hydroxy-2,3-quinuclidinedicarboxylic acid, which was obtained as a colorless mobile oil, readily soluble in organic solvents. B.p. 142° (1.2 mm). The substance crystallized on standing, m.p. 104-105° (from ether). Yield 13.5 g.

Found %: C 57.68; H 7.79; N 5.30. $C_{13}H_{21}O_5N$. Calculated %: C 57.56; H 7.75; N 5.17.

b) The butyl ester of 3-hydroxy-3-cyano-2-quinuclidinecarboxylic acid (7.5 g) was treated in the same manner as described in a). We obtained 1.6 g of 3-quinuclidinone and 3 g of the diethyl ester of 3-hydroxy-2,3-quinuclidinedicarboxylic acid. B.p. 145° (1.3 mm), m.p. 104-105°.

Hydrochloride of 3-hydroxy-2,3-quinuclidinedicarboxylic acid. One gram of the diethyl ester of 3-hydroxy-2,3-quinuclidinedicarboxylic acid was refluxed with 10 ml of dilute hydrochloric acid (1 : 1) for 5 hr. The hydro-

chloric acid solution was evaporated in vacuo, while the residue was dissolved in 10 ml of alcohol and the alcohol solution was treated with 100 ml of ether. The obtained precipitate was filtered and dried. We obtained 0.6 g (65%) of the hydrochloride of 3-hydroxy-2,3-quinuclidinedicarboxylic acid as colorless crystals, readily soluble in water and alcohol, and insoluble in ether. M.p. 126° (decomp.).

Found %: N 5.23; Cl 14.11. $C_9H_{13}O_5N \cdot HCl$. Calculated %: N 5.56; Cl 14.15.

Diethyl ester of Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid (Va). A solution of 15.7 g of the diethyl ester of 3-hydroxy-2,3-quinuclidinedicarboxylic acid in 150 ml of thionyl chloride was refluxed for 30 hr. Then the thionyl chloride was vacuum-distilled, while the residue was dissolved in 50 ml of water, treated with 50 ml of 50% potassium carbonate solution, and the alkaline solution was extracted with ether. The ether extract was dried, the solvent was distilled off, and the residue was vacuum-distilled. We obtained 10.9 g (74.5%) of the substance, which proved to be a quite mobile oil with a greenish tinge, readily soluble in organic solvents. B.p. 130° (0.5 mm).

The hydrochloride was obtained as colorless crystals, soluble in water and in alcohol, and insoluble in ether. M.p. 148.5° (from acetone).

Found %: C 53.68; H 6.99; N 4.92; Cl 12.35. $C_{13}H_{19}O_4N$. Calculated %: C 53.88; H 6.91; N 4.83; Cl 12.28.

Δ^2-Dehydro-2,3-quinuclidinedicarboxylic acid (Vb). A solution of 2.1 g of the diethyl ester of Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid in 20 ml of dilute hydrochloric acid (1 : 1) was refluxed for 5 hr. The solution was decolorized by treatment with carbon, and the filtrate was evaporated in vacuo. We obtained 1.63 g (99%) of Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid as colorless crystals, readily soluble in water, difficultly soluble in alcohol, and insoluble in acetone and in ether. M.p. 240° (decompn., from aqueous alcohol).

Found %: C 54.72; H 5.45; N 6.92. $C_9H_{11}O_4N$. Calculated %: C 54.82; H 5.55; N 7.10.

Hydrochloride of Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid. A solution of 0.35 g of Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid in 10 ml of a 23% alcoholic solution of hydrogen chloride was treated with 50 ml of absolute ether. We obtained 0.25 g of the hydrochloride of Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid as colorless, hygroscopic crystals, easily hydrolyzed by water.

Found %: N 5.91, 5.88; Cl 14.91, 14.78. $C_9H_{12}O_4NCl$. Calculated %: N 5.99; Cl 15.20.

Hydrochloride of 2,3-quinuclidinedicarboxylic acid (VIa). A mixture of 1.3 g of Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid, 25 ml of 4% hydrochloric acid and 0.2 g of platinum oxide was shaken with hydrogen at room temperature. When one mole of hydrogen had been absorbed, the platinum black was filtered, and the filtrate was evaporated in vacuo. We obtained 1 g (76.5%) of the hydrochloride of 2,3-quinuclidinedicarboxylic acid. M.p. 138° (decompn.). Colorless crystals, soluble in water, alcohol, and acetone, and insoluble in ether.

Found %: C 42.37; H 5.98; N 5.36. $C_9H_{13}O_4N \cdot HCl \cdot H_2O$. Calculated %: C 42.6; H 6.36; N 5.53.

Diethyl ester of 2,3-quinuclidinedicarboxylic acid (VIb). Ten grams of the hydrochloride of 2,3-quinuclidinedicarboxylic acid was refluxed with 100 ml of a 10% alcoholic solution of hydrogen chloride for 5 hr. The solvent was vacuum-distilled, while the residue was dissolved in 50 ml of water, followed by the addition of 50 ml of a 50% potassium carbonate solution, and the whole was extracted with chloroform. The chloroform solution was dried, the solvent was evaporated, and the residue was vacuum-distilled. We obtained 8 g (74%) of the diester as a colorless mobile oil, readily soluble in organic solvents. B.p. 115° (0.4 mm).

Found %: C 60.71; H 8.24; N 5.86. $C_{13}H_{21}O_4N$. Calculated %: C 61.2; H 8.25; N 5.53.

2,3-Bis(hydroxymethyl)quinuclidine (VIIa). A solution of 3.65 g of the diethyl ester of 2,3-quinuclidinedicarboxylic acid in 70 ml of anhydrous ether was added with stirring to a suspension of 1.1 g of aluminum lithium hydride in 50 ml of anhydrous ether. The mixture was heated at ether boil for 3 hr. Then the mixture was treated under cooling with 2.2 ml of water, after which the inorganic salts were filtered and washed well with chloroform. The ether-chloroform extract was evaporated in vacuo, and the residue was vacuum-distilled. B.p. 150° (0.3 mm). Colorless viscous oil, readily soluble in water and in organic solvents. Yield 1.4 g (58%).

The hydrochloride was obtained as colorless crystals, readily soluble in water and alcohol, insoluble in ether, and highly hygroscopic.

Found %: N 6.92; Cl 17.25. $C_9H_{17}O_2N \cdot HCl$. Calculated %: N 6.76; Cl 17.15.

2,3-Bis(acetoxymethyl)quinuclidine (VIIb). A mixture of 1.3 g of 2,3-bis(hydroxymethyl)quinuclidine, 5 ml of acetyl chloride and 15 ml of anhydrous chloroform was refluxed for 5 hr. The reaction mass was evaporated, followed by treatment of the residue with 50% potassium carbonate solution, and then extraction of the whole with chloroform. The chloroform solution was dried, the solvent was distilled off, and the residue was vacuum-distilled. We obtained 1.94 g (70%) of the diacetate as a colorless, fairly viscous oil, which proved to be soluble in organic solvents, and insoluble in water. B.p. 138-140° (0.6 mm).

Found %: C 60.98; H 8.36; N 5.35. $C_{13}H_{21}O_4N$. Calculated %: C 61.18; H 8.24; N 5.49.

3-Carbethoxy-2-quinuclidinecarboxylic acid (VIII). A solution of 2 g of the diethyl ester of 2,3-quinuclidinedicarboxylic acid in 38 ml of water was allowed to stand at room temperature for 7 days. Then the water was vacuum-distilled, while the residue was dried by treating it 3 times with benzene, with removal of the benzene each time by distillation. The residue was triturated with ether, and the obtained crystals were filtered and washed several times with ether in order to remove any starting material. We obtained 1.6 g (83.5%) of 3-carbethoxy-2-quinuclidinecarboxylic acid. The compound was obtained as a white hygroscopic powder, readily soluble in water, alcohol, and chloroform, and insoluble in ether. M.p. 188-189° (decompn.).

Found %: C 57.62; H 7.70; N 6.15. $C_{11}H_{17}O_4N \cdot H_2O$. Calculated %: C 58.15; H 7.49; N 6.17.

SUMMARY

The synthesis of 2,3-quinuclidinedicarboxylic acid was accomplished by starting from the ethyl and butyl esters of 3-oxo-2-quinuclidinecarboxylic acid, via the analogous esters of 3-hydroxy-3-cyano-2-quinuclidinecarboxylic acid, the ethyl ester of 3-hydroxy-2,3-quinuclidinedicarboxylic acid, and Δ^2-dehydro-2,3-quinuclidinedicarboxylic acid.

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SOME DERIVATIVES OF 5-NITRO- AND 5-AMINO-3-INDAZOLECARBOXYLIC ACID

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
pp. 3255-3257, October, 1961

As a continuation of our investigations for the purpose of finding physiologically active compounds in the indazole series [1] we investigated the possibility of synthesizing 5-amino-3-aminomethylindazole, starting with the nitrile of 3-indazolecarboxylic acid [2]. Treatment of the latter with nitric acid (d 1.46) gave the nitrile of nitro-3-indazolecarboxylic acid, which, in order to prove the position of the nitro group, was subjected to hydrolysis, and the resulting nitro-3-indazolecarboxylic acid was decarboxylated.

Determination of the melting point of the obtained nitroindazole revealed that this substance is 5-nitroindazole [3], with m.p. 208-209°. The nitrile of 5-nitro-3-indazolecarboxylic acid was converted in conventional manner to the thioamide. The use of hydrazine hydrate in the presence of skeletal nickel catalyst, in an alcohol medium, proved to be the most convenient way of reducing the nitro group. The nitrile of 5-amino-3-indazolecarboxylic acid was subjected to acetylation. Attempts to reduce the nitrile group in the diacetyl derivative using metallic sodium in anhydrous alcohol, hydrogen in the presence of platinum oxide or skeletal nickel catalyst in alcoholic ammonia solution at 100 atm and room temperature, or $LiAlH_4$ in ether, all proved unsuccessful: the starting substance was recovered unchanged. When the reduction of the nitrile of 1-acetyl-4-acetamido-3-indazolecarboxylic acid was run in the presence of skeletal nickel catalyst in alcoholic ammonia solution at 100 atm and 100° we obtained a substance that melted above 300°, which we were unable to identify.

EXPERIMENTAL

Nitrile of 5-nitro-3-indazolecarboxylic acid. Fifteen grams of 3-indazolecarbonitrile was gradually added to 120 ml of nitric acid (d 1.46) at 10-15°. Then the reaction mass was kept for 10 min at 15° and poured over ice. After recrystallization from methyl alcohol we obtained 14.7 g (74.5%) of a colorless, crumbly, crystalline powder with m.p. 234-236°.

Found %: C 51.07; H 2.20; N 30.16. $C_8H_4O_2N_4$. Calculated %: C 51.06; H 2.14; N 29.78.

5-Nitro-3-indazolecarboxylic acid. A mixture of 3.8 g of the 3-indazolecarbonitrile and 25 ml of a 10% aqueous NaOH solution was heated under reflux, with stirring, for 1 hr. Then the solution was poured into 100 ml of hot water and acidified with dilute hydrochloric acid until acid to Congo. The acid that separated here was extracted with ether in a Soxhlet apparatus. After removal of the ether the residue was recrystallized from methyl alcohol.

5-Nitro-3-indazolecarboxylic acid is a slightly yellow crystalline powder with m.p. 262° (decompn.), soluble in ethyl acetate, alcohol, and alkalies.

Found %: C 46.00; H 2.59; N 20.05. $C_8H_5O_4N_3$. Calculated %: C 46.38; H 2.43; N 20.29.

5-Nitroindazole. 5-Nitro-3-indazolecarboxylic acid (0.6 g) was heated at 250° until the evolution of carbon dioxide ceased. 5-Nitroindazole was obtained as slightly yellow needles with m.p. 206-208° (from methyl alcohol). From the literature [2]: m.p. 208-209°.

Found %: C 51.67; H 3.16. $C_7H_5O_2N_3$. Calculated %: C 51.53; H 3.08.

Nitrile of 5-amino-3-indazolecarboxylic acid. A solution of 9 ml of hydrazine hydrate in 10 ml of methanol was gradually added to a mixture, composed of 8 g of 5-nitro-3-indazolecarbonitrile in 240 ml of methanol and 6.7 g of skeletal nickel catalyst paste, heated to 60-65°, and then the reaction mass was kept at this temperature, with stirring, for 1 hr. After this reaction mixture was cooled, filtered to remove the catalyst, the filtrate was evaporated to 1/3 volume, and the residue was diluted with an equal volume of ice water. The nitrile of 5-amino-3-indazole-

carboxylic acid separated as a slightly yellow powder with m.p. 207-209° (from alcohol). The compound is readily soluble in alcohol, dioxane, and dilute acetic acid, and is insoluble in ether and in benzene. Yield 4.7 g (70%).

Found %: C 60.62; H 3.87; N 34.71. $C_8H_6N_4$. Calculated %: C 60.74; H 3.82; N 35.42.

Nitrile of 2-acetyl-5-acetamido-3-indazolecarboxylic acid. Two grams of 5-amino-3-indazolecarbonitrile in 10 ml of acetic anhydride was heated for 1 hr on the water bath. The solid reaction mass was treated with ice water and the precipitate was filtered. We obtained 1.8 g of 1-acetyl-5-acetamido-3-indazolecarbonitrile as a colorless, finely crystalline powder with m.p. 264-266° (from hexyl alcohol), difficultly soluble in the common organic solvents.

Found %: C 59.20; H 4.32; N 23.06. $C_{12}H_{10}O_2N_4$. Calculated %: C 59.49; H 4.16; N 23.13.

Thioamide of 5-nitro-3-indazolecarboxylic acid. A stream of dry hydrogen sulfide was passed into a solution of 1 g of 5-nitro-3-indazolecarbonitrile in 15 ml of alcoholic ammonia solution at a temperature not exceeding 25°. A yellow crystalline substance began to deposit within 30 min. The hydrogen sulfide passage was continued for another 30 min, after which the substance was filtered and recrystallized twice from alcohol. The thioamide of 5-nitro-3-indazolecarboxylic acid crystallizes as yellow needles with m.p. 217° (decompn.). The compound is soluble in alcohol and ethyl acetate, and is insoluble in ether.

Found %: N 25.61; S 14.71. $C_8H_6O_2N_4S$. Calculated %: N 25.21; S 14.42.

SUMMARY

3-Indazolecarbonitrile was nitrated and it was shown that the nitro group enters the 5-position. The nitro group was reduced to the amino group, but attempts to reduce the nitrile group in 5-amino-3-indazolecarbonitrile proved unsuccessful.

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IMIDAZOLE SERIES

XI. SYNTHESIS OF (2-IMIDAZOLYLTHIO)ACETIC ACIDS

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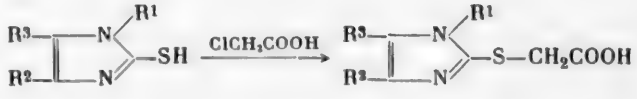
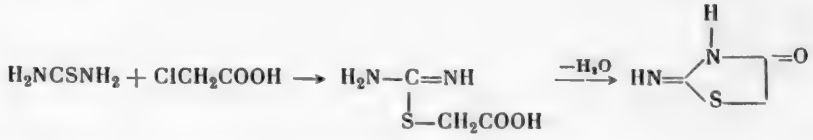
Original article submitted November 2, 1960

We recently described the synthesis of (5-carboxy-2-imidazolylthio)- and (4,5-dicarboxy-2-imidazolylthio)-acetic acids [1]. As a continuation of this work it seemed of interest to obtain a series of (2-imidazolylthio)acetic acids and study some of their physicochemical properties and biological action.

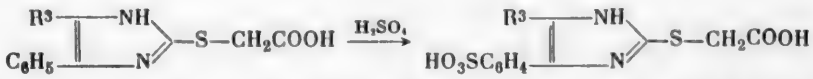
As starting materials for the synthesis of these compounds we used the 4(5)-aryl-, 4,5-diaryl- and 1,4,5-triaryl-2-mercaptoimidazoles [2, 3]. To eliminate the possibility of forming the esters of the (2-imidazolylthio)acetic acids, as had occurred in the previously described cases [1], the reaction of the above indicated 2-mercaptoimidazole derivatives with either chloro- or bromoacetic acid was not run in alcohols, but instead it was run in glacial acetic acid. In this solvent the alkylation of the mercapto group in the 2-mercaptoimidazoles went smoothly to yield the hydrohalides of the (2-imidazolylthio)acetic acids, from which the acids themselves (I-VI) could be easily isolated by treatment with sodium acetate.



Since the 2-mercaptoimidazoles are cyclic thiourea derivatives, the synthesis of (2-imidazolylthio)acetic acids is analogous to the formation of pseudothiohydantoic acid (A) when thiourea is reacted with chloroacetic acid [4, 5]. The properties of the (2-imidazolylthio)acetic acids obtained by us differ from the properties of pseudothiohydantoic acid in that the latter, even on gentle heating in a solvent, readily cleaves a molecule of water, cyclizing to pseudothiohydantoin (B) [5].



The (2-imidazolylthio)acetic acids are very stable compounds not only when heated in solvents, but also when treated with certain water-removing agents. The synthesized acids (I-III) do not cyclize to imidazo[2,1-c]triazolidin-3-ones, even when heated for a long time with either glacial acetic acid or conc. sulfuric acid. Only sulfonation of the benzene ring occurred when acids (I) and (II) were heated with conc. sulfuric acid, in which connection the dibasic acids: [4(5)-p-sulfophenyl-2-imidazolylthio]acetic acid (VII) and [4(5)-p-sulfophenyl-5(4)-phenyl-2-imidazolylthio]acetic acid (VIII) were obtained.



It is interesting to mention that only one benzene ring sulfonates when acid (III) is heated with conc. sulfuric acid at 100° although in the starting compound both phenyl groups are equivalent. This is explained by the fact that the introduction of the sulfo group into an organic compound retards its further sulfonation [6]. In the present case

No. of compound	R¹	R³	R⁵	Method of synthesis	Yield, (in %)	Recrystallization solvent	Color and shape of crystals
(I)	H	C_6H_5	H	a,b	96.3—99	Ethanol	Colorless needles of prism
(II)	H	$C_6H_4NO_2$-p	H	a	97.7	Water	Yellow needles
(III)	H	C_6H_5	C_6H_5	a,b	96.6—99.6	Dilute hydrochloric acid	Colorless needles of prism
(IV)	C_6H_5	C_6H_5	C_6H_5	a,b	92.8—76.2	Glacial acetic acid	Colorless crystals
(V)	$C_6H_4CH_3$-p	C_6H_5	C_6H_5	b	99	Ethanol	Colorless plates
(VI)	$C_6H_4OC_2H_5$-p	C_6H_5	C_6H_5	b	94.1	Ethanol	Colorless prisms
(VII)	H	$C_6H_4SO_3H$-p	H	—	69.9—78.9	Water	Colorless plates
(VIII)	H	$C_6H_4SO_3H$-p	C_6H_5	—	—	Water	Colorless prisms

* Found %: H_2O 3.14. Calculated 3.70. Hydrochloride – colorless plates (from glacial acetic acid) with m.p. 218-219° (decompn.). Found %: Cl 13.17. $C_{11}H_{10}O_2N_2S \cdot HCl$. Calculated %: Cl 13.47. Hydrobromide – colorless prisms (from glacial acetic acid) with m.p. 203-204° (decompn.). Found %: Br 25.27. $C_{11}H_{10}O_2N_2S \cdot HBr$. Calculated %: Br 25.36. Sulfate – colorless prisms (from water) with m.p. 106-107.5° (decompn.). Found %: N 8.82; H_2O 9.38. $C_{11}H_{10}O_2N_2S \cdot H_2SO_4 \cdot 1.5H_2O$. Calculated %: N 8.43; H_2O 8.79. Picrate – yellow prisms (from ethanol) with m.p. 79-80°. Found %: N 14.20; H_2O 3.80. $C_{11}H_{10}O_2N_2S \cdot C_6H_3O_7N_3 \cdot H_2O$. Calculated %: N 14.55; H_2O 3.74.

** Hydrobromide – colorless prisms (from acetone) with m.p. 96-97°. Found %: Br 18.37; H_2O 8.35. $C_{17}H_{14}O_2N_2S \cdot HBr \cdot 2H_2O$. Calculated %: Br 18.36; H_2O 8.28. Sodium salt – colorless plates (from water), not melting up to 280°. Found %: N 7.06; H_2O 14.75. $C_{17}H_{13}O_2N_2SNa \cdot 3H_2O$. Calculated %: N 7.25; H_2O 13.98.

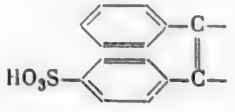
*** Hydrochloride – colorless crystals (from glacial acetic acid) with m.p. 207.5-208° (decompn.). Found %: Cl 8.29. $C_{23}H_{18}O_2N_2S \cdot HCl$. Calculated %: Cl 8.38. Hydrobromide – colorless crystals (from glacial acetic acid) with m.p. 212.5-213.5° (decompn.). Found %: Br^- 17.04. $C_{23}H_{18}O_2N_2S \cdot HBr$. Calculated %: Br 17.07.

**** Hydrobromide – colorless crystals (from glacial acetic acid) with m.p. 219-220° (decompn.). Found %: Br 16.70. $C_{24}H_{20}O_2N_2S \cdot HBr$. Calculated %: Br 16.60.

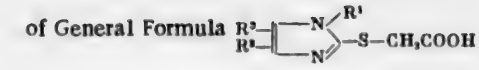
***** Hydrobromide– colorless prisms (from glacial acetic acid) with m.p. 211.5-212° (decompn.). Found %: N 5.56; Br 15.75. $C_{25}H_{22}O_3N_2S \cdot HBr$. Calculated %: N 5.48; Br 15.62.

****** Found %: H_2O 5.40. Calculated 5.42.

the influence of the sulfo group, present in one benzene ring, is easily extended to the other aromatic ring due to the presence of a system of conjugated bonds.



The structure of sulfo acid (VII) was proved by its oxidation with alkaline potassium permanganate, in which connection the monosodium salt of p-sulfobenzoic acid [7] was obtained. The position of the sulfo group in acid (VIII) was not established, although by analogy with (VII) it could be assumed that also in this compound the sulfo group is found in the para-position of one of the benzene rings.

of General Formula 

M. p. (decompn.)	Empirical formula	Found (%)				Calculated (%)			
		C	H	N	S	C	H	N	S
178.5—179.5°	$C_{11}H_{10}O_2N_2S \cdot 0.5H_2O$*	54.62	4.91	11.29	13.06	54.29	4.56	11.51	13.18
205—206	$C_{11}H_9O_4N_3S$	47.66	3.32	15.06	11.43	47.31	3.25	15.05	11.48
210.5—211.5	$C_{17}H_{14}O_2N_2S$**	65.68	4.20	8.94	9.78	65.79	4.55	9.03	10.33
151—152	$C_{23}H_{18}O_2N_2S$***	71.67	5.11	7.07	8.64	71.48	4.69	7.25	8.30
156—157	$C_{24}H_{20}O_2N_2S$****	71.79	4.54	6.64	8.18	71.97	5.03	6.99	8.01
185—186	$C_{25}H_{22}O_3N_2S$*****	69.60	4.98	6.47	7.21	69.74	5.15	6.51	7.45
Do not melt up to 280°	$C_{11}H_{10}O_5N_2S_2 \cdot H_2O$******	39.73	3.51	8.40	19.62	39.78	3.64	8.43	19.29
Do not melt up to 280°	$C_{17}H_{14}O_5N_2S_2 \cdot 0.5H_2O$	51.35	3.56	6.96	16.06	51.12	3.78	7.01	16.06

The properties and analyses of the synthesized (2-imidazolylthio)acetic acids are given in the table.

EXPERIMENTAL

[4(5)-Phenyl-2-imidazolylthio]acetic acid (I). a) A mixture of 8.8 g of 4(5)-phenyl-2-mercaptoimidazole [2] and 4.7 g of chloroacetic acid in 25 ml of glacial acetic acid was heated carefully until a stormy reaction began. After heating at the boil for 3 min the solution began to deposit a white precipitate. The mixture was refluxed for 15 min, after which it was cooled, and the precipitate was filtered, washed with glacial acetic acid, then with ether, and dried. We obtained 13 g of the hydrochloride of acid (I) as colorless plates with m.p. 217-219° (decompn.). The hydrochloride is readily soluble in water and the lower alcohols, and very slightly soluble in acetone, dichloroethane, and glacial acetic acid. Decomposition of the hydrochloride with aqueous sodium acetate solution gave acid (I) as colorless needles or prisms, insoluble in organic solvents.

The same procedure was used to obtain acids (II), (III) and (IV). In the case of (II), the precipitate that separated on conclusion of heating the solution was the free acid (II), and not the hydrochloride, which is explained by the fact that compound (II) is not basic in character. The isolation of acids (III) and (IV) was accomplished by adding sodium acetate to an acetic acid solution of their hydrochlorides, followed by pouring of the solutions into water.

b) A solution of 1.76 g of 4(5)-phenyl-2-mercaptoimidazole and 1.5 g of bromoacetic acid in 5 ml of glacial acetic acid was heated and then worked up as described above (method a). We obtained 3.12 g of the hydrobromide of (I) as colorless prisms, m.p. 203-204° (decompn.), and readily soluble in water. Decomposition of the hydrobromide with aqueous sodium acetate solution gave the free base (I) (table). This same procedure was used to obtain acids (III-VI). Because the hydrobromides of acids (IV-VI) are insoluble in water, the free acids were isolated by the addition of sodium acetate to an acetic acid solution of the hydrobromide, followed by pouring of the mixture into water.

[4(5)-p-Sulfophenyl-2-imidazolylthio]acetic acid (VII). a) A solution of 1 g of the hydrochloride of acid (I) in 7 ml of 96% sulfuric acid was heated on the boiling water bath for 3.5 hr, after which it was cooled and poured into 75 ml of water; the obtained precipitate was filtered, washed with water, and dried. We obtained 0.97 g of substance, which did not melt up to 280°. Colorless plates (from water), readily soluble in aqueous solutions of sodium acetate and sodium bicarbonate, difficultly soluble in boiling water, and insoluble in organic solvents. The substance crystallizes with one molecule of water.

b) A solution of 1 g of acid (I) in 7 ml of 96% sulfuric acid was heated at 70-75° for 10 min, after which it was cooled and poured into 50 ml of water. The obtained precipitate was filtered, washed with water, and dried. We obtained 0.94 g of acid (VII) as colorless plates, not melting up to 280°.

To prove the sturcture of (VII), a solution of 0.72 g of the substance, 3 g of potassium permanganate and 8.5 ml of 40% NaOH solution in 60 ml of water was refluxed for 2 hr, after which the excess oxidizing agent was destroyed by the addition of several drops of methanol. The manganese dioxide precipitate was filtered and washed twice with hot water (20 ml). The mother liquor was acidified with hydrochloric acid until acid to Congo and the solvent was evaporated on the water bath. The dry residue was dissolved in 25 ml of boiling water, and the solution was filtered and cooled. We obtained 0.35 g (72.2%) of the monosodium salt of p-sulfobenzoic acid as long colorless prisms (from water) or plates (from saturated sodium chloride solution) [7].

[4(5)-p-Sulfophenyl-5(4)-phenyl-2-imidazolylthio]acetic acid (VIII). A solution of 1.55 g of acid (III) in 7 ml of 96% sulfuric acid was heated on the boiling water bath for 1.5 hr, after which it was cooled and poured into 35 ml of water; the obtained precipitate was filtered and washed with water. The sample taken for analysis was purified by dissolving the substance in hot aqueous sodium acetate solution, followed by the addition of hydrochloric acid. The compound was obtained as fine colorless prisms (from water), not melting up to 280°. The prisms are difficultly soluble in boiling water, insoluble in cold water and most organic solvents, and readily soluble in solutions of alkalies, sodium bicarbonate, and sodium acetate.

SUMMARY

A series of (2-imidazolylthio)acetic acids was obtained by the reaction of 4(5)-aryl-, 4,5-diaryl- and 1,4,5-triaryl-2-mercaptoimidazoles with chloro- and bromoacetic acids.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

IMIDAZOLE SERIES

XII. SYNTHESIS OF ESTERS AND HYDRAZIDES OF (2-IMIDAZOLYLTHIO)-ACETIC ACIDS

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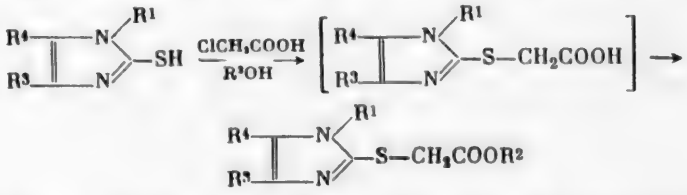
In a previous paper [1] it was mentioned that even the short heating of the esters of 2-mercaptoimidazolecarboxylic acids with bromoacetic acid in methanol or ethanol leads to the formation of the hydrobromides of the corresponding esters of (2-imidazolylthio)acetic acids. We decided to make a more detailed study of this reaction and to utilize the ease with which the (2-imidazolylthio)acetic acids are esterified to obtain the esters, and from the latter – the hydrazides of the corresponding acids. The synthesized compounds, especially the hydrazides of the acids, possessed some interest for the evaluation of their biological properties.

As starting compounds we used the [4(5)-aryl-, [4,5-diaryl- and [1,4,5-triaryl-2-imidazolylthio]acetic acids [2].

It was established that those (2-imidazolylthio)acetic acids which exhibit an amphoteric character and are capable of forming stable hydrohalides in alcohol solutions are easily esterified at the carboxyl group of the acetic acid moiety. Thus, when the hydrochloride of [4(5)-phenyl-2-imidazolylthio]acetic acid was refluxed with anhydrous methyl, ethyl, isopropyl, n-butyl, isoamyl and primary n-hexyl alcohols we obtained the hydrochlorides of the corresponding esters of [4(5)-phenyl-2-imidazolylthio]acetic acid (I, IV, VI-IX) in good yields (74-96%). Esters (XIV) and (XVI) were synthesized in a similar manner from the hydrobromide of (4,5-diphenyl-2-imidazolylthio)-acetic acid and the hydrochloride of (1,4,5-triphenyl-2-imidazolylthio)acetic acid, respectively.

As was to be expected, these acids are not esterified when hydrogen halide is not present in the reaction medium. For example, even the prolonged refluxing of [4(5)-phenyl-2-imidazolylthio]acetic acid with anhydrous isopropyl alcohol failed to result in the formation of ester (V); the starting material was recovered unchanged.

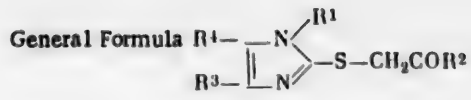
A simple and convenient way of obtaining the esters of (2-imidazolylthio)acetic acids is to heat 2-mercaptoimidazoles with either chloro- or bromoacetic acid under reflux in the appropriate alcohols. In this case the intermediate (2-imidazolylthio)acetic acids are not isolated. The yield of the esters is 94-96% of theory, based on the starting 2-mercaptoimidazoles. This procedure (b) was used to obtain esters (I), (IV) and (VI).



However, this method is not applicable to obtaining the esters of those (2-imidazolylthio)acetic acids where, due to the presence of electron-acceptor substituents in the imidazole ring, the compounds exhibit strongly acidic properties and do not form hydrohalides. Thus, when 4(5)-p-nitrophenyl-2-mercaptoimidazole was heated with chloroacetic acid under reflux in anhydrous ethanol for 8 hr (refluxing interrupted overnight) we obtained a complex mixture, consisting of the starting material, [4(5)-p-nitrophenyl-2-imidazolylthio]acetic acid, and its ethyl ester (the latter in small amount). Only the prolonged refluxing of [4(5)-p-nitrophenyl-2-imidazolylthio]acetic acid with a 10% solution of hydrogen chloride in anhydrous alcohol gave ester (XI) in low yield (63.6%). In such cases a more reliable method is the direct reaction of 2-mercaptoimidazoles with the esters of either chloro- or bromoacetic acid. Thus, compounds (X) and (XII), and also esters (II), (IV) and (XIII) were obtained using this procedure.

No. of compound	R^1	R	R^3	R^4	Yield (in %)	M. p.
(I)	H	OCH_3	C_6H_5	H	95.7	123—124.5° (ethanol + acetone)
(II)	H	OCH_3	C_6H_5	H	95.8—99.6	133—134 (decompn.) (methanol or ethanol)
(III)	H	OCH_3	C_6H_5	H	—	159—160 (ethanol)
(IV)	H	OC_2H_5	C_6H_5	H	94—95.3	141—143 (dioxane)
(V)	H	OC_3H_7-iso	C_6H_5	H	—	104—105(decompn.) (aqueous isopropyl alcohol)
(VI)	H	OC_3H_7-iso	C_6H_5	H	92—88.8	166—167.5(decompn.) (ethanol + acetone)
(VII)	H	OC_4H_9-n.	C_6H_5	H	87.3	125—125.5 (decompn.) (ethanol + acetone)
(VIII)	H	OC_5H_{11}-iso	C_6H_5	H	91.1	149—150 (ethanol + acetone)
(IX)	H	OC_6H_{13}-n.	C_6H_5	H	74.3	144—145 (ethanol + acetone)
(X)	H	OCH_3	$C_6H_4NO_2$-p	H	—	149—150(decompn.) (methanol)
(XI)	H	OC_2H_5	$C_6H_4NO_2$-p	H	63.6	146—147 (ethanol)
(XII)	H	OC_2H_5	$C_6H_4NO_2$-p	H	95.8	211—212 (decompn.) (glacial acetic acid)
(XIII)	H	OC_2H_5	C_6H_5	C_6H_5	70	116.5—117 (ethanol)
(XIV)	H	OC_4H_9-n.	C_6H_5	C_6H_5	75.5	123—124 (acetone + ether)
(XV)	C_6H_5	OC_2H_5	C_6H_5	C_6H_5	—	115—118 (decompn.) (ethanol)
(XVI)	C_6H_5	OC_2H_5	C_6H_5	C_6H_5	90	178—180 (decompn.) (ethanol + acetone)
(XVII)	H	$NHNH_2$	C_6H_5	H	89.8	142.5—143.5(decompn.) (20% ethanol)
(XVIII)	H	$NHNH_2$	$C_6H_4NO_2$-p	H	84.2—90	198—199 (decompn.)
(XIX)	H	$NHNH_2$	C_6H_5	C_6H_5	—	162—163 (decompn.) (ethanol)
(XX)	C_6H_5	$NHNH_2$	C_6H_5	C_6H_5	90.2	119—120(decompn.) (butanol)

* Found %: H_2O 6.80. Calculated %: H_2O 5.95.

General Formula 

Empirical formula	Found (%)					Calculated (%)				
	C	H	N	S	Cl	C	H	N	S	Cl
$C_{12}H_{12}O_2N_2S \cdot HCl \cdot H_2O$ * Colorless crystals	47.32	4.92	9.27	10.81	12.25	47.60	4.99	9.25	10.59	11.71
$C_{12}H_{12}O_2N_2S \cdot HBr \cdot H_2O$ Colorless plates	42.10	4.50	7.87	9.32	22.81 (Br)	41.51	4.35	8.07	9.23	23.01 Br
$C_{12}H_{12}O_2N_2S \cdot C_6H_3O_7N_3$ Yellow prisms	—	—	14.70	—	—	—	—	14.67	—	—
$C_{13}H_{14}O_2N_2S \cdot HCl \cdot 0.5\ H_2O$ Colorless plates	50.89	5.04	9.00	10.49	11.14	50.73	5.24	9.10	10.42	11.52
$C_{14}H_{16}O_2N_2S$ Colorless prisms	60.56	5.73	9.84	11.54	—	60.85	5.84	10.10	11.60	—
$C_{14}H_{16}O_2N_2S \cdot HCl$ Colorless plates	—	—	—	—	11.75	—	—	—	—	11.33
$C_{15}H_{18}O_2N_2S \cdot HCl$ Colorless crystals	55.23	5.65	8.60	9.37	11.01	55.13	5.86	8.57	9.81	10.85
$C_{16}H_{20}O_2N_2S \cdot HCl$ Colorless crystals	56.26	6.87	7.89	9.23	10.58	56.37	6.91	8.22	9.41	10.40
$C_{17}H_{22}O_2N_2S \cdot HCl$ Colorless prisms	57.49	6.47	8.05	8.69	10.13	57.53	6.53	7.90	9.04	9.99
$C_{12}H_{11}O_4N_3S$ Yellow prisms	—	—	14.14	10.78	—	—	—	14.33	10.93	—
$C_{13}H_{13}O_4N_3S$ Yellow prisms	—	—	13.79	10.83	—	—	—	13.68	10.43	—
$C_{13}H_{13}O_4N_3S \cdot HCl$ Curved yellow prisms	45.64	4.03	11.99	9.52	10.42	45.42	4.10	12.22	9.33	10.31
$C_{19}H_{18}O_2N_2S$ Colorless prisms	67.40	5.18	8.17	9.11	—	67.44	5.36	8.28	9.48	—
$C_{21}H_{22}O_2N_2S \cdot HBr$ Colorless crystals	—	—	6.33	7.36	18.42 Br	—	—	6.26	7.17	17.86 Br
$C_{25}H_{22}O_2N_2S$ Colorless needles	72.68	5.45	6.84	8.02	—	72.44	5.35	6.76	7.74	—
$C_{25}H_{22}O_2N_2S \cdot HCl$ Polyhedral colorless prisms	—	—	6.09	—	7.84	—	—	6.21	—	7.86
$C_{11}H_{12}ON_4S$ Colorless prisms	53.24	4.72	22.39	12.71	—	53.21	4.87	22.57	12.91	—
$C_{11}H_{11}O_3N_5S$ Yellow crystals	45.32	3.56	23.95	10.68	—	45.04	3.78	23.88	10.93	—
$C_{17}H_{16}ON_4S$ Colorless prisms	63.01	5.23	16.92	10.20	—	62.96	4.96	17.28	9.88	—
$C_{23}H_{20}ON_4S$ Colorless needles	68.43	4.92	14.28	7.99	—	68.97	5.03	13.99	8.01	—

The synthesis of the hydrazides of the [4(5)-phenyl-, [4(5)-p-nitrophenyl-, [4,5-diphenyl- and [1,4,5-triphenyl-2-imidazolylthio]acetic acids (XVII-XX) was accomplished in conventional manner – by reacting the appropriate esters of the acids (or their hydrochlorides) with hydrazine hydrate in either alcohol or aqueous alcohol solution.

EXPERIMENTAL

Ethyl ester of [4(5)-phenyl-2-imidazolylthio]acetic acid (XXI). a) A solution of 2.7 g of [4(5)-phenyl-2-imidazolylthio]acetic acid hydrochloride [2] in 27 ml of anhydrous ethyl alcohol was refluxed for 3.5 hr, after which the solvent was distilled off in vacuo to a small volume, followed by the addition of 30 ml of ether to the residue. The obtained white precipitate was filtered, washed with ether, and dried. We obtained 2.86 g of (IV). The same method used to obtain compounds (I, VI-IX, XIV, XVI). To synthesize ester (XIV) we used the hydrobromide of (4,5-diphenyl-2-imidazolylthio)acetic acid [2], while in all of the other cases we used the hydrochlorides of the starting acids. In the synthesis of compound (VIII) we used 25 ml of isoamyl alcohol per gram of acid hydrochloride, while in all of the other cases the alcohols were taken in the proportion of 10 ml of alcohol per gram of (2-imidazolylthio)-acetic acid hydrochloride. The reflux time ranged from 3.5 to 6 hr.

b) A solution of 1.76 g of 4(5)-phenyl-2-mercaptoimidazole [3] and 1 g of chloroacetic acid in 40 ml of anhydrous ethanol was refluxed for 3 hr, after which the alcohol was removed by vacuum-distillation, while the crystalline residue was washed with ether and dried. We obtained 2.81 g of (IV). The mixed melting point with the (IV) prepared by method (a) was not depressed.

Esters (II) and (VI) were prepared by this same procedure. Bromoacetic acid was used in the synthesis of (II).

c) A mixture of 3.52 g of 4(5)-phenyl-2-mercaptoimidazole and 2.55 g of ethyl chloroacetate in 25 ml of ethyl alcohol was refluxed for 40 min, after which the solvent was removed by vacuum-distillation, while the residue was washed with ether and dried. We obtained 5.7 g of (IV). Decomposition of the hydrochloride with aqueous potassium carbonate solution gave the free base – the ethyl ester of [4(5)-phenyl-2-imidazolylthio]acetic acid (XXI) – as a viscous colorless liquid, readily soluble in organic solvents, and insoluble in water. The methyl ester of [4(5)-phenyl-2-imidazolylthio]acetic acid (XXII), obtained by the decomposition of its salt (I), exhibits analogous properties.

Using the same procedure, and starting with the 4(5)-phenyl-, 4(5)-p-nitrophenyl- and 4,5-diphenyl-2-mercaptoimidazoles [3, 4] and the appropriate chloroacetic acid esters, we obtained compounds (II), (X), (XII) and (XIII). Methyl bromoacetate was used in the synthesis of esters (II) and (X).

Ethyl ester of [4(5)-p-nitrophenyl-2-imidazolylthio]acetic acid (XI). d) A mixture of 5 g of [4(5)-p-nitrophenyl-2-imidazolylthio]acetic acid [2] and 150 ml of a 10% hydrogen chloride solution in anhydrous ethanol was refluxed for 16 hr (interrupted overnight), after which the solution was cooled, and the obtained precipitate was filtered, washed with aqueous potassium carbonate solution, then with water, and dried. We obtained 3.5 g of (XI). The substance is difficultly soluble in the cold in most organic solvents, and is insoluble in water.

Hydrazide of [4(5)-phenyl-2-imidazolylthio]acetic acid (XVII). A hot solution of 2.7 g of (IV) in 45 ml of 50% aqueous ethanol was treated with 5.4 ml of 85% hydrazine hydrate and the mixture was heated up to the boil. Then the solution was cooled to 0° and the obtained white precipitate was filtered, washed with a little water, and dried. We obtained 2.02 g of the compound.

The mixed melting point with the starting substance was depressed.

Hydrazide of [4(5)-p-nitrophenyl-2-imidazolylthio]acetic acid (XVIII). a) A suspension of 3.8 g of ester (X) in 50 ml of alcohol was treated with 15 ml of 85% hydrazine hydrate solution, in which connection the ester dissolved immediately and a dark red solution was formed, from which a yellow precipitate began to deposit in 5-7 min. The mixture was refluxed for 10 min, after which it was allowed to stand overnight. The obtained precipitate was filtered, washed with alcohol, then with ether, and dried. We obtained 3.2 g of yellow crystals, which proved to be insoluble in water and most organic solvents. Starting with ester (XIII), we obtained the hydrazide of (4,5-diphenyl-2-imidazolylthio)acetic acid (XIX) in a similar manner.

b) A suspension of 0.8 g of (XII) in 15 ml of alcohol was treated with 3.2 ml of 85% hydrazine hydrate solution, in which connection a blood-red solution was obtained immediately. The solution was allowed to stand at 18-20° for 48 hr, after which the obtained yellow-green precipitate was filtered, washed with alcohol, then with ether, and dried. We obtained 0.61 g of the compound, which did not depress the melting point when mixed with the substance prepared by method (a).

Hydrazide of (1,4,5-triphenyl-2-imidazolylthio)acetic acid (XX). A hot solution of the hydrochloride of ester (XVI) in 10 ml of ethanol was treated with 5 ml of 85% hydrazine hydrate solution and the mixture was allowed to stand overnight at 18-20°. Then the solution was evaporated in a dish on the water bath, and the obtained precipitate was filtered, washed with water, and dried. We obtained 1.2 g of the compound, which proved to be difficultly soluble in ethanol, and insoluble in water. The mixed melting point with the free base of the starting ester (XV) was depressed.

The properties and analyses of the obtained compounds are given in the table.

SUMMARY

A series of esters and hydrazides of the [4(5)-aryl-, [4,5-diaryl- and [1,4,5-triaryl-2-imidazolylthio]acetic acids were synthesized.

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IMIDAZOLE SERIES

XIII. REACTION OF ACETIC ANHYDRIDE WITH (2-IMIDAZOLYLTHIO)-ACETIC ACIDS AND THEIR ESTERS

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
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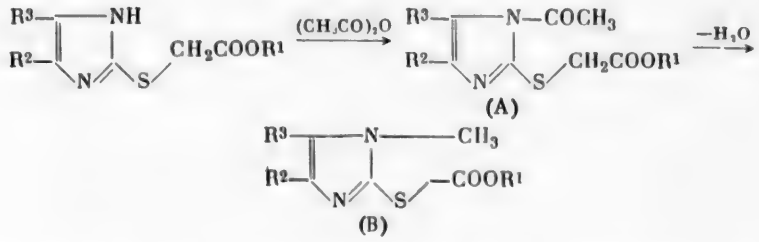
The reaction of acetic anhydride with 4(5)-aryl-2-β-oxoalkyl(aryl)-mercaptoimidazoles had been studied previously and it was established that these compounds are acetylated with extreme ease on the imino group of the imidazole ring to yield 1-acetyl-5-aryl-2-β-oxoalkyl(aryl)-mercaptoimidazoles. The latter on further heating with acetic anhydride and sodium acetate (and sometimes in the absence of the latter) are cyclized to 3-methyl-5-arylimidazo[2,1-b]thiazol-2-yl alkyl(aryl) ketones [1]. The preparation of thianaphthene derivatives by the dehydration of (o-acetylphenylthio)acetic acid using either acetic anhydride or NaOH is also described in the literature [2]. In these cases the closure of both the thiazole and the thiophene ring takes place via the elimination of water, involving the oxygen atom of the acetyl group and the hydrogen atoms of the methylene group found between the sulfur and either the carbonyl or the carboxyl group.

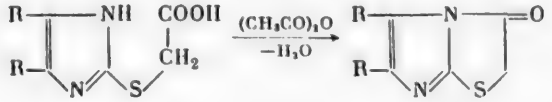
In expanding these studies it seemed of interest to us to examine the reaction of acetic anhydride with the (2-imidazolylthio)acetic acids and their esters, the synthesis of which was described in our previous papers [3, 4]. We were interested in isolating the N-acetyl derivatives of these acids and esters (A). If in compounds (A) the methylene group proves to be as reactive as in the 2-β-oxoalkyl(aryl)-mercaptoimidazoles or (o-acetylphenylthio)acetic acid, then it becomes possible to obtain the previously unavailable derivatives of 3-methylimidazo [2,1-b]thiazol-2-yl carboxylic acid (B).



(A)

(B)

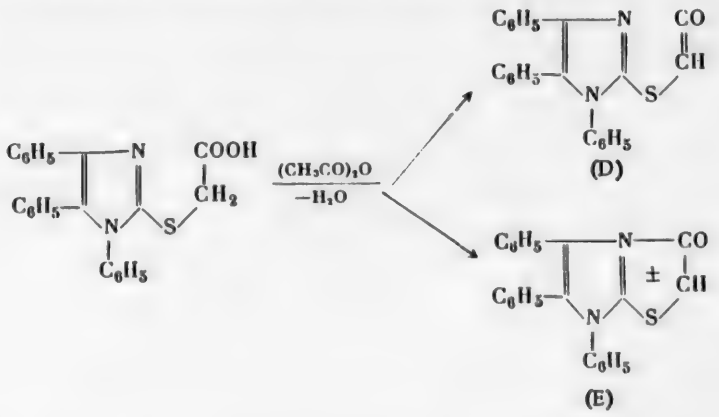
It was established that the reaction of acetic anhydride with the (2-imidazolylthio)acetic acids and their esters goes in a variable manner. In some cases the acetic anhydride behaves like a strong dehydrating agent, and in other cases as an acetylating agent. When the 4(5)-substituted and 4,5-disubstituted derivatives of (2-imidazolylthio)acetic acid are reacted with acetic anhydride they undergo dehydration with the formation of bicyclic compounds – the imidazo [2,1-b]thiazoldin-3-ones (C). Thus, compounds (VII-IX) were obtained from the [4(5)-phenyl-, [4(5)-p-nitrophenyl- and [4,5-diphenyl-2-imidazolylthio]acetic acids (see Experimental).



(C)

It is indicated in the literature [5] that similar properties are possessed by (2-benzimidazolylthio)acetic acid, which is cyclized to benzimidazo[2,1-b]thiazolidin-3-one when treated with acetic anhydride and pyridine.

The N-substituted derivatives of (2-imidazolylthio)acetic acid, which, it would seem, should be indifferent toward acetic anhydride, also react with it with the elimination of water. Thus, the treatment of (1,4,5-triphenyl-2-imidazolylthio)acetic acid with acetic anhydride gave a crystalline compound (X), which contained one molecule of water less than the starting acid. Based on the tenets of the classical structure theory, it is possible to assign the structure of ketone (D) to compound (X). It is more probable that this compound has the meso-ionic structure (E), which can be regarded as being an imidazo[3,2-b]thiazole derivative.



The British investigators [5], who prepared several anhydro compounds – derivatives of (1-methyl-2-imidazolthio)acetic and (1-alkyl(aryl-2-benzimidazolylthio)acetic acids, believe that the properties of these compounds are best explained by meso-ionic structures. Apparently, in order to ascertain the actual structure of anhydro compounds of this type it is necessary to make a more exhaustive study of their chemical and physico-chemical properties.

Its acylating action is manifested when acetic anhydride is reacted with the esters of the 4(5)-monosubstituted and 4,5-disubstituted derivatives of (2-imidazolylthio)acetic acid. The N-acetyl derivatives of the esters of (2-imidazolylthio)acetic acids (A) are formed as a reaction result. Acetylation of the methyl, ethyl and isopropyl esters of [4(5)-phenyl-2-imidazolylthio]acetic acid, the methyl and ethyl esters of [4(5)-p-nitrophenyl-2-imidazolylthio]-acetic acid, and the ethyl ester of (4,5-diphenyl-2-imidazolylthio)acetic acid gave compounds (I-VI), the more important properties and analyses of which are given in the table. These compounds when heated with acetic anhydride and sodium acetate are not dehydrated to esters (B).

The ethyl ester of (1,4,5-triphenyl-2-imidazolylthio)acetic acid, in contrast to the corresponding acid, does not react with acetic anhydride.

The acetylation of the esters of [4(5)-aryl-2-imidazolylthio]acetic acids can yield two isomers: the esters of (1-acetyl-4-aryl- and (1-acetyl-5-aryl-2-imidazolylthio)acetic acids. In all cases only one compound was obtained by us. By analogy with the synthesis of 1-acetyl-5-aryl-2-β-oxoalkyl(aryl)mercaptoimidazoles [1], the structure of which was unequivocally shown, we postulate that the isolated compounds (I-V) are the esters of [1-acetyl-5-phenyl(p-nitrophenyl)-2-imidazolylthio]acetic acids.

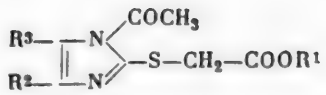
Formation of the (C) compounds takes place via an intramolecular acylation of the imino group of the imidazole ring by the acetic acid radical, linked through sulfur to the imidazole ring. Based on the above considerations, compounds (VII) and (VIII) are apparently the 5-phenyl- and 5-p-nitrophenylimidazo[2,1-b]thiazolidin-3-ones, respectively.

The properties and analyses of the obtained compounds are given in the table.

EXPERIMENTAL

Methyl ester of (1-acetyl-5-phenyl-2-imidazolylthio)acetic acid (I). A solution of 1.08 g of methyl [4(5)-phenyl-2-imidazolylthio]acetate [4] in 1.8 ml of acetic anhydride was allowed to stand at 18-20° for 5 min, in which connection a white precipitate deposited. The mixture was then treated with 10 ml of ether, and the precipitate was filtered, washed with ether, and dried. We obtained 0.83 g of the compound, which proved to be soluble in most organic solvents, very slightly soluble in ether, and insoluble in water. Compounds (II) and (III) have the same solubility properties.

Synthesized Compounds of General Formula



No. of compound	R^1	R^2	R^3	Yield, in %	Color and shape of crystals	M. p.	Empirical formula	Found %				Calculated %			
								C	H	N	S	C	H	N	S
(I)	CH_3	H	C_6H_5	65.9	Colorless prisms	141—142° (from methanol)	$C_{14}H_{14}O_3N_2S$	57.90	4.64	9.36	10.80	57.91	4.86	9.65	11.04
(II)	C_2H_5	H	C_6H_5	—	Colorless plates	135.5—136.5 (from ethanol)	$C_{15}H_{16}O_3N_2S$	58.95	5.24	9.32	10.42	59.19	5.29	9.24	10.53
(III)	$CH(CH_3)_2$	H	C_6H_5	64.5	Colorless plates	154—155 (from isopropyl alcohol)	$C_{16}H_{18}O_3N_2S$	60.76	5.97	9.03	9.66	60.36	5.70	8.80	10.07
(IV)	CH_3	H	$C_6H_4NO_2$-p	99.6	Yellow needles	233—234 (decomp.) (from glacial acetic acid)	$C_{14}H_{13}O_5N_3S$	50.49	3.68	12.39	9.29	50.14	3.91	12.53	9.56
(V)	C_2H_5	H	$C_6H_4NO_2$-p	88.7	Yellow needles	176—176.5 (from glacial acetic acid)	$C_{15}H_{15}O_5N_3S$	51.22	4.51	12.17	9.32	51.56	4.33	12.03	9.18
(VI)	C_2H_5	C_6H_5	C_6H_5	52.2	Colorless prisms	118.5—119.5(decomp.) (from isopropyl alcohol)	$C_{21}H_{20}O_3N_2S$	66.32	5.06	7.58	8.47	66.29	5.30	7.36	8.43

Ethyl ester of (1-acetyl-5-phenyl-2-imidazolylthio)acetic acid (II). Obtained in the same manner as compound (I), with the exception that the reaction was run at 70-80°. The time of heating was 4 min.

Isopropyl ester of (1-acetyl-5-phenyl-2-imidazolylthio)acetic acid (III). A mixture of 1.8 g of isopropyl [4(5)-phenyl-2-imidazolylthio]acetate [4], 0.6 g of anhydrous sodium acetate and 20 ml of acetic anhydride was refluxed for 35 min (the last 5 min in the presence of carbon). Then the solution was filtered, the acetic anhydride was vacuum-distilled, and the residue was transferred from the flask to a filter, washed with ether, then with water, again with ether, and dried. We obtained 1.2 g of the compound. The starting ester was recovered unchanged if the reaction was run in refluxing acetic anhydride in the absence of sodium acetate.

Methyl ester of (1-acetyl-5-p-nitrophenyl-2-imidazolylthio)acetic acid (IV). A solution of 2.55 g of methyl [4(5)-p-nitrophenyl-2-imidazolylthio]acetate [4] in 30 ml of acetic anhydride was refluxed for 3 min, after which it was cooled and worked up as in the isolation of ester (I). Yield 2.9 g. The substance is difficulty soluble in alcohol and glacial acetic acid, and is insoluble in water. Esters (V) and (VI) have the same solubility properties.

Ethyl ester of (1-acetyl-5-p-nitrophenyl-2-imidazolylthio)acetic acid (V). A solution of 6.1 g of the hydrochloride of the ethyl ester of [4(5)-p-nitrophenyl-2-imidazolylthio]acetic acid [4] in 80 ml of acetic anhydride was refluxed for 20 min (the last 5 min with carbon), after which it was filtered and cooled, and the obtained precipitate was filtered, washed with a little acetone, then with ether, and dried. We obtained 4.5 g of the compound. Evaporation of the mother liquor to a small volume, followed by washing the residue first with acetone and then with ether, gave an additional gram of the substance.

Ethyl ester of (1-acetyl-4,5-diphenyl-2-imidazolylthio)acetic acid (VI). A solution of 4.1 g of ethyl (4,5-diphenyl-2-imidazolylthio)acetate [4] in 27 ml of acetic anhydride was refluxed for 1.5 hr (the last 10 min with carbon), after which it was filtered and the anhydride was removed by vacuum-distillation to a small volume of the residue. The residue on cooling deposited a precipitate, which was washed with ether, filtered, and dried. We obtained 2.4 g of the compound. The mixed melting point with the starting ester was depressed. The starting compound was recovered unchanged if the reaction was run in refluxing acetic anhydride for 5-7 min.

5-Phenylimidazo[2,1-b]thiazolidin-3-one (VII). A solution of 2 g of [4(5)-phenyl-2-imidazolylthiol]acetic acid [3] in 3 ml of acetic anhydride was refluxed for 3 min, after which it was cooled, in which connection a precipitate deposited. The mixture was then treated with 30 ml of ether, and after several hours the precipitate was filtered, washed with ether, and dried. We obtained 1.7 g (97.1%) of the compound, m.p. 127-135° (decompn.). Colorless prisms (from anhydrous ethanol) with m.p. 156-157° (decompn.) The substance is soluble in organic solvents, and is insoluble in water. The mixed melting point with the starting material (m.p. 178.5-179.5°) was 147-149° (decompn.).

Found %: C 60.95; H 3.86; N 13.07; S 14.40. $C_{11}H_8ON_2S$. Calculated %: C 61.08; H 3.73; N 12.96; S 14.83.

5-p-Nitrophenylimidazo[2,1-b]thiazolidin-3-one (VIII). A solution of 4.3 g of [4(5)-p-nitrophenyl-2-imidazolylthio)]acetic acid [3] in 140 ml of acetic anhydride was refluxed for 75 min (the last 5 min in the presence of carbon), after which it was filtered and cooled. The obtained yellow precipitate was filtered, washed with glacial acetic acid, then with ether, and dried. We obtained 2.7 g of substance with m.p. 233-234° (decompn.). Evaporation of the mother liquor to a small volume and washing the precipitate with ether gave an additional 0.6 g of the same substance with m.p. 213-215° (total yield 3.3 g, or 82.5%). The compound was obtained as fine yellow prisms, collecting in clusters (from glacial acetic acid). M.p. 235.5-236° (decompn.). The substance is very lightly soluble in most of the organic solvents and is insoluble in water.

Found %: C 50.45; H 2.52; N 15.51; S 12.44. $C_{11}H_7O_3N_3S$. Calculated %: C 50.56; H 2.70; N 16.08; S 12.27.

5,6-Diphenylimidazo[2,1-b]thiazolidin-3-one (IX). A solution of 3.1 g of (4,5-diphenyl-2-imidazolylthio)-acetic acid [3] in 15 ml of acetic anhydride was refluxed for 5 min, after which it was cooled, and the obtained precipitate was filtered, washed with glacial acetic acid, then with ether, and dried. We obtained 2.64 g of product with m.p. 204-205°. Evaporation of the mother liquor to a small volume and washing the precipitate with ether gave an additional 0.22 g of the substance with m.p. 200-201° (total yield 2.86 g, or 99.9%). Short, polyhedral colorless prisms (from glacial acetic acid) with m.p. 206-207° (decompn.), soluble in organic solvents, and insoluble in water. The mixed melting point with the starting material (m.p. 210.5-211.5°) was 190-191° (decompn.).

Found %: C 69.53; H 4.04; N 9.49; S 11.00. $C_{17}H_{12}ON_2S$. Calculated %: C 69.83; H 4.17; N 9.58; S 10.96.

Anhydro compound, derivative of (1,4,5-triphenyl-2-imidazolylthio)acetic acid (X). To 8 ml of acetic anhydride, heated to 70-80°, was added 3.86 g of (1,4,5-triphenyl-2-imidazolylthio)acetic acid [3]. The acid went into solution quickly, and soon a white crystalline precipitate began to deposit from the solution. The mixture was then cooled and treated with 40 ml of acetone, after which the precipitate was filtered, washed with acetone, then with ether, and dried. We obtained 2.47 g (67.1%) of the compound, which darkened at 200°, and decomposed at 205-210°. The sample for analysis was purified by dissolving the substance in glacial acetic acid, after which the solution was poured into acetone. The compound was obtained as slightly pink crystals with m.p. 205-208° (decompn.), insoluble in water, hydrochloric acid, caustic alkali solutions, and most of the common organic solvents. The compound is readily soluble in both acetic anhydride and acetic acid, in which connection it decomposes when the solution is heated. The mixed melting point with the starting material (m.p. 151-152°) was 133-136° (decompn.).

Found %: C 74.75; H 4.51; N 7.35; S 8.49. $C_{23}H_{16}ON_2S$. Calculated %: C 74.99; H 4.38; N 7.60; S 8.70.

SUMMARY

1. The reaction of acetic anhydride with (2-imidazolylthio)acetic acids and their esters was studied. It was established that although the compounds have a similar structure, they react differently with acetic anhydride.

2. (2-Imidazolylthio)acetic acids when treated with acetic anhydride cleave a molecule of water, cyclizing to imidazo[2,1-b]-thiazolidin-3-ones.

3. The reaction of the esters of (2-imidazolylthio)acetic acids with acetic anhydride leads to the formation of the corresponding acetyl derivatives, acetylated on the imino group of the imidazole ring.

4. The esters of the N substituted (2-imidazolylthio)acetic acid derivatives do not react with acetic anhydride, whereas the corresponding acids form anhydro compounds.

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PREPARATION OF THE NITRILE AND AMIDE OF NICOTINIC ACID

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Original article submitted September 22, 1960

Earlier we had reported [1] the preparation of the nitriles of the β- and γ-pyridinecarboxylic acids by the vapor-phase oxidation of the β- and γ-picolines with atmospheric oxygen in the presence of ammonia and vanadium pentoxide.

Subsequent studies revealed that the yield of the nitrile of nicotinic acid depends on the composition and method of preparing the catalyst. The action of a number of catalysts was studied. Thus, using the vanadates of tin or iron in the presence of potassium sulfate, the results of oxidizing β-picoline differed but slightly from those obtained using vanadium pentoxide alone. The yield of nicotinonitrile reached a maximum of only 65.6%, while that of nicotinamide reached only 36.5%. It was found that the best catalyst is vanadium pentoxide, deposited on aluminum oxide, and containing potassium sulfate as additive. With this catalyst the yield of nicotinonitrile was 93.6%, based on reacted β-picoline, and that of nicotinamide was 64.9%.

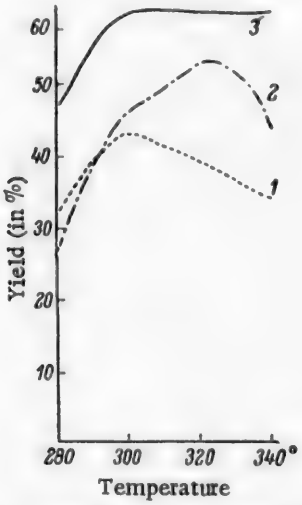

Fig. 1. Yield of nicotinamide as a function of the temperature and the catalyst. 1) Iron vanadate; 2) tin vanadate; 3) vanadium pentoxide + potassium sulfate.

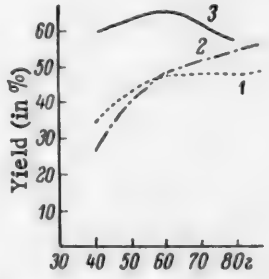

Fig. 2. Yield of nicotinamide as a function of the charge (in g) of β-picoline per liter of catalyst per hour. The designations are the same as in Fig. 1.

The yield of nicotinamide as a function of the temperature and the catalyst is shown in Fig. 1, while the yield of nicotinamide as a function of the charge in grams of β-picoline per liter of catalyst per hour is shown in Fig. 2.

EXPERIMENTAL

Preparation of catalyst. A mixture of 7.5 g of ammonium metavanadate and 4 g of potassium sulfate was dissolved in 200 ml of water with heating. Then 150 ml (bulk volume) of aluminum oxide was added to the hot solution and the mixture was evaporated with stirring, after which it was dried for 2 hr at 150°. Prior to use the catalyst was activated by blowing with air at 400° for 3-4 hr.

Preparation of nicotinonitrile. The oxidation of β-picoline to nicotinonitrile was run in an excess of atmospheric oxygen and ammonia. Prior to admittance into the reactor, the air was dried by passage through a column

filled with calcium chloride and a wash bottle containing conc. sulfuric acid, and then through U-shaped tubes containing glass wool. A charge of 80 ml of freshly prepared catalyst was placed in the middle of the reactor; a bed of broken tile was placed both above and below this catalyst layer. The temperature in the electrically heated reactor was raised to 320°. The air, passing through a calibrated vaporizer at a rate of 2.5 liters/min, was saturated with β-picoline vapors, after which it entered the preheater, where it was mixed with ammonia and heated to 320°. The condensed reaction products were absorbed in water contained in a receiver, which was connected to traps. We obtained an aqueous ammoniacal solution of nicotinonitrile and unreacted β-picoline (19%). The yield of nicotinonitrile was 93.6% (based on reacted β-picoline). M.p. 56-57° (from water).

Found %: C 69.20; H 3.68; N 22.88, 26.90. $C_6H_4N_2$. Calculated %: C 69.23; H 3.85; N 26.92.

Preparation of nicotinamide [2]. A mixture of 100 ml of an aqueous ammoniacal solution of 7.69 g of nicotinonitrile, 5 g of KOH and 30 ml of 10% perhydrol solution was heated at 42° for 2 hr, after which 5 g of ammonium chloride was added and the formed amide was extracted with 200 ml of ethyl acetate. The yield was 6.06 g (64.9%). M.p. 129.5-130°.

SUMMARY

A study was made of the reaction conditions for the catalytic, vapor-phase oxidation of β-picoline and the most effective catalyst was selected, giving a nicotinonitrile yield of 93.6%, and a nicotinamide yield of 64.9%, based on reacted β-picoline.

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2-CYCLOPROPYL- AND 2-PROPENYL-FURAN AND -THIOPHENE

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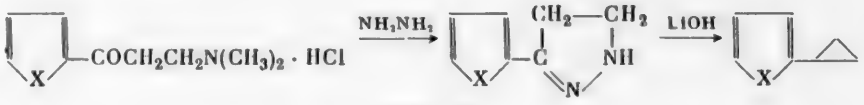
Original article submitted November 9, 1960

The N. M. Kizhner method, involving the decomposition of pyrazolines, is extensively used in the synthesis of compounds of the cyclopropane series, in which connection 1-methyl-2-(2-furyl)cyclopropane [1] and 2-cyclopropylfuran [2] were also obtained by this method.

In the present study we became convinced that when 2-furylpyrazoline, synthesized from 2-furylacrolein, is decomposed by the method given in [2] a 2-cyclopropylfuran is obtained, which, based on the Raman spectrum data, contains a substantial amount of 2-propenylfuran as impurity, in which connection the latter cannot be removed either by treatment with potassium permanganate or by reaction with 2,4-dinitrobenzenesulfenyl chloride [3].

Next we aminomethylated 2-acetylfuran, and also 2-acetylthiophene, and then converted the obtained Mannich bases to the corresponding pyrazolines. Decomposition of the latter in the presence of lithium hydroxide [4] gave respectively 2-cyclopropylfuran and 2-cyclopropylthiophene, devoid of ethylene derivatives as impurities, and in better yields (respectively 53.5% and 51%).



X = O, S.

As regards 2-propenylfuran, then it has been prepared by the decomposition of 2-furylpyrazoline [2], but chiefly [5-8] it has been prepared by the catalytic dehydration of ethyl-2-furylcarbinol over aluminum oxide at 400-450°; in the latter case the hydrogenation product – 2-propylfuran [6] – is also formed in nearly equal amount.

We ran the catalytic dehydration of ethyl-2-furylcarbinol under milder conditions, at 275°, and obtained as reaction product a 2-propenylfuran that was free of 2-propylfuran as impurity.

We obtained 2-propenylthiophene in good yield by the pyrolysis of the acetate of ethyl-2-thienylcarbinol (instead of the described [9] dehydration of the carbinol by heating with either potassium bisulfate or potassium hydroxide).

EXPERIMENTAL

2-Cyclopropylfuran. a) A hot solution of 42 g of 1-(2-furyl)-3-dimethylamino-1-propanone hydrochloride (obtained by the method of [10]: m.p. 177-178°; literature data: m.p. 178° [11]) in 100 ml of anhydrous methanol was added in 20 min to a solution of 8 g of NaOH and 25 ml of hydrazine hydrate in 50 ml of anhydrous methanol, after which the mixture was refluxed for 4 hr, followed by separation of the precipitate and vacuum-distillation (8 mm) of the filtrate to remove solvent and unchanged hydrazine hydrate. The oily residue was dissolved in ether, the ether solution was washed with water, dried, and after removal of the ether by vacuum-distillation we obtained 16.5 g (59%) of 2-furylpyrazoline as a pale yellow oil.

b) Portions composed of 4 g of 2-furylpyrazoline and 0.5 g of dry lithium hydroxide were heated in a small Wurtz flask until gas evolution began (around 250°) and 2.1 g of condensate was obtained. The condensates were combined, treated with 2 N acetic acid, washed with water, extracted with ether, and the extracts were dried. After distilling off the ether the residue distilled at 126-128° (756 mm), and had n^{20}_D 1.4765; when the material was distilled through a column (40 theoretical plates) with a cushion of decalin we obtained 7.5 g (53.5%) of 2-cyclopropylfuran:

B.p. 126.8-127.8° (761 mm), n^{20}_D 1.4792, d_4^{20} 0.9762, MR_D 31.39. $C_7H_8OF_2$ Δ. Calculated: 31.54.

Literature data [2]: b.p. 127-129° (747 mm), n^{20}_D 1.4825, d_4^{20} 0.9461, MR_D 32.59.

The Raman spectrum confirmed the absence of 2-propenylfuran as impurity.

2-Cyclopropylthiophene. a) A solution of 25 g of 1-(2-thienyl)-3-dimethylamino-1-propanone hydrochloride, m.p. 179°, obtained as described in [10], in hot anhydrous methanol was added to a mixture of 14 ml of hydrazine hydrate and 4 g of NaOH in 50 ml of anhydrous methanol, and the mixture was refluxed for 3 hr. The reaction was worked up as described above to give 11 g (64%) of 2-thienylpyrazoline as a yellowish oil.

b) A mixture of 11 g of 2-thienylpyrazoline and 0.7 g of dry lithium hydroxide was heated in a Wurtz flask to 190-200° (start of gas evolution), then gradually to 250°, after which it was kept at this temperature for 2 hr. We obtained 5.3 g of condensate; the material was extracted with ether, washed with 2 N acetic acid, then with water, and dried. After distilling off the solvent the residue distilled at 44.5-45.5° (6 mm), n^{20}_D 1.5459, d_4^{20} 1.0533. To remove any possible ethylene derivative, 5 g of the material and 0.5 g of 2,4-dinitrobenzenesulfenyl chloride in 50 ml of absolute benzene was refluxed for 3 hr, after which the benzene was distilled off and the residue was distilled. We obtained 4.6 g (51%) of 2-thienylcyclopropane:

B.p. 44.0-44.5° (6 mm), n^{20}_D 1.5451, d_4^{20} 1.0587, MR_D 37.09. $C_7H_8SF_2\Delta$. Calculated: 37.60.

Found %: C 67.57, 67.78; H 6.35, 6.52. C_7H_8S. Calculated %: C 67.73; H 6.49.

The Raman spectrum confirmed the absence of 2-propenylthiophene as impurity.

2-Propenylfuran. From 35 g of ethyl-2-furylcarbinol (b.p. 67-67.5° at 7 mm, n^{20}_D 1.4760 [7]), passed in 10-15 g portions over aluminum oxide (internal tube diameter 20 mm, layer length 25 cm) at 275°, at a rate of 10-11 drops/min, in a nitrogen stream, we obtained (after distillation over sodium) 13.4 g (40%):

B.p. 131.5-132.5° (763 mm), n^{20}_D 1.5091, d_4^{20} 0.9450, MR_D 34.17. $C_7H_8OF_3$. Calculated 32.57.

Literature data: b.p. 132-133° (752 mm), n^{20}_D 1.5098, d_4^{20} 0.9457 [8].

2-Propenylthiophene. a) A mixture of 10 g of ethyl-2-thienylcarbinol (b.p. 93.5° at 7 mm, n^{20}_D 1.5350, d_4^{20} 1.1092 [12]) and 20 ml of acetic anhydride in 30 ml of pyridine was heated for 2 hr on the water bath, and after appropriate treatment we obtained 9.8 g (82%) of ethyl-2-thienylcarbinyl acetate:

B.p. 93-94° (6 mm), n^{20}_D 1.5007, d_4^{20} 1.0313, MR_D 49.35. $C_9H_{12}O_2SF_2$. Calculated 50.87.

b) Using a nitrogen stream, 9.8 g of the acetate was passed at a rate of 4-6 drops/min and a temperature of 450° through a tube (internal diameter 10 mm) filled with glass wool (layer length 20 cm). The condensate was worked up in appropriate manner to give 4.6 g (72%) of 2-propenylthiophene:

B.p. 51.5-52° (7 mm), n^{20}_D 1.5732, d_4^{20} 1.0299, MR 39.70. $C_7H_8SF_3$. Calculated 38.62.

Literature data: b.p. 63° (14 mm), n^{20}_D 1.5713 [13]; b.p. 46-47° (7 mm), n^{25}_D 1.5705 [12].

SUMMARY

When decomposed in the presence of lithium hydroxide, the pyrazolines obtained by reacting hydrazine hydrate with the Mannich bases derived from 2-acetofuran and 2-acetothiophene give respectively 2-cyclopropylfuran and 2-cyclopropylthiophene, which are respectively free of 2-propenylfuran and 2-propenylthiophene.

The synthesis of 2-propenylfuran and 2-propenylthiophene can be successfully accomplished by subjecting the corresponding secondary alcohols to dehydration on aluminum oxide catalyst at a temperature not exceeding 275°, and also by subjecting the acetates of these alcohols to pyrolysis at 450°.

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FURAN SERIES

XVIII. 2,5-BIS(N-ALKYLAZOMETHINE)- AND 2,5-BIS(ARYLAZOMETHINE)-FURANS

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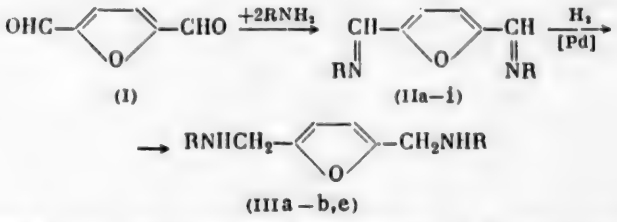
Original article submitted October 24, 1960

2,5-Furandicarboxaldehyde (I), the synthesis of which was described in a previous communication [1], was used in the present study to synthesize some bis-azomethine compounds and diamines of the furan series. The reaction of (I) with primary aliphatic and aromatic amines yields the corresponding Schiff bases (II) in quite high yields. Catalytic hydrogenation of the Schiff bases (II) in the presence of palladium gave us the corresponding 2,5-bis(alkylaminomethyl)furans (III).

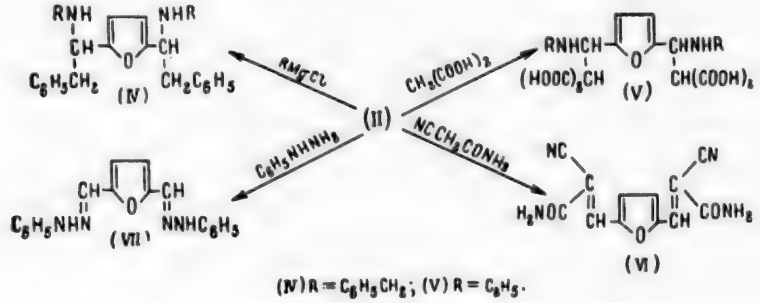


(I) (IIa–i) (IIIa–b,e)

a) R = CH_3; b) R = C_2H_5; c) R = n-C_4H_9; d) R = $C_6H_5CH_2$; e) R = CH_3–C_6H_3O; f) R = C_6H_5; g) R = o-$CH_3C_6H_4$; h) R = p-$CH_3C_6H_4$; i) R = β-$C_{10}H_7$.

The reaction of benzylmagnesium chloride with 2,5-bis(N-benzylazomethine)furan (IId) gave 2,5-bis(α-benzylamino-β-phenethyl)furan (IV). The reaction of 2,5-bis(N-ethylazomethine)furan (IIb) with malonic acid, as the result of the active methylene group of the acid adding to the C = N bond, gives 2,5-bis(α-ethylamino-β,β-dicarboxyethyl)furan (V) (92% yield). However, replacing the malonic acid by the amide of cyanoacetic acid (monoamide of the mononitrile of malonic acid) gave 2,5-bis(β-cyano-β-carbamoylvinyl)furan (VI) in 72% yield. The latter is apparently obtained as the result of the elimination of amine from the initially formed addition product of cyanoacetamide to the C = N bond of (IIb).

The reaction of phenylhydrazine with the studied bis-azomethine compounds of the furan series (II) gave in all cases the bis-phenylhydrazone of 2,5-furandicarboxaldehyde (VII) in 85-90% yield, which was formed as the result of transamination, caused by the poor solubility of (VII) in alcohol.



(IV) R = $C_6H_5CH_2$; (V) R = C_6H_5.

When reacted with picric acid in absolute ether, the bis-azomethine compounds of the furan series (II) give picrates that are exceedingly hygroscopic and quite unstable compounds, especially the picrates of the bases obtained from (I) and aliphatic amines; they are easily hydrolyzed at the C = N bond by atmospheric moisture to give the picrate of the primary amine and 2,5-furandicarboxaldehyde (I).

EXPERIMENTAL

1. Preparation of Bis-Azomethine Compounds of Furan Series

For reaction we took equimolar amounts of 2,5-furandicarboxaldehyde (I) and primary amine (because of their volatility, methylamine, ethylamine and n-butylamine were taken in excess); except for the synthesis of (IIf) and (IIg), the reaction was run in alcohol solution. Short (15-20 min) heating on the water bath (45-50°) was sufficient to obtain complete reaction. After distilling off the alcohol the liquid reaction products were vacuum-distilled, while the solid products were recrystallized from a suitable solvent. With the exception of (IIb) and (IIc), the obtain bis-azomethine compounds are yellow* crystalline substances. The 2,5-bis(ethyl)- (IIb) and 2,5-bis(butylazomethine)furan (IIc) are yellowish oils, that darken when stored and are quite difficult to purify. The constants and the yields of the obtained bases are given in the table.

2. Reduction of Bis-Azomethine Compounds of Furan Series

2,5-Bis(methylaminomethyl)furan (IIIa). A mixture of 0.5 g of (I) in 20 ml of alcohol and 2 ml of a 25% alcoholic methylamine solution was hydrogenated in the cold, in the presence of palladium (5%) deposited on barium sulfate. The calculated amount of hydrogen (179 ml NTP) was absorbed in 2 hr. After removal of the catalyst, the alcohol was distilled off, while the residue was vacuum-distilled to give 0.3 g (50%) of product, b.p. 104-105° (7 mm), $n^{20}D$ 1.4945.

The dipicrate was prepared in absolute ether, m.p. 149-150° (from alcohol). The mixed melting point with the dipicrate of 2,5-bis(methylaminomethyl)furan, obtained by a different procedure [3], was not depressed.

2,5-Bis(ethylaminomethyl)furan (IIIb). For reaction we took 0.35 g of (I) and 0.26 g of ethylamine in 20 ml of alcohol. The calculated amount (134 ml NTP) of hydrogen was absorbed. We obtained 0.3 g (60%) of product, b.p. 109-110° (4 mm), $n^{20}D$ 1.4820.

The dipicrate was obtained as described above; m.p. 105-106° (from alcohol). The mixed melting point with the dipicrate of (IIIb), obtained by a different procedure [3], was not depressed.

2,5-Bis(butylaminomethyl)furan (IIIc). For reaction we took 0.16 g of 2,5-furandicarboxaldehyde (I) and 0.36 g of n-butylamine in 20 ml of alcohol. The calculated amount of hydrogen (68 ml NTP) was absorbed. We obtained 0.18 g (60%) of product; b.p. 107-108°(0.5 mm), $n^{20}D$ 1.4800.

Dipicrate, m.p. 82-83° (from alcohol). The mixed melting point with the dipicrate of (IIIc), obtained by a different procedure [3], was not depressed.

2,5-Bis(furylaminomethyl)furan (IIIe). For reaction we took 1.0 g of (I) and 1.6 g of furfurylamine in 20 ml of alcohol. The amount of hydrogen absorbed was 258 ml (NTP) (calculated 363 ml). We obtained 0.7 g (30%) of product; b.p. 150-151° (0.5 mm), $n^{20}D$ 1.5358. The compound does not form a crystalline picrate.

The picrolonate was obtained in absolute ether, m.p. 216-217° (from anhydrous methyl alcohol).

Found %: N 14.65. $C_{26}H_{28}O_9N_6$. Calculated %: N 14.80.

3. Reaction of Bis-Azomethine Compounds of Furan Series

A solution of 0.8 g of the furan bis-azomethine compound (IId) in 150 ml of absolute ether was added dropwise in 1 hr to the benzylmagnesium chloride (prepared from 0.46 g of magnesium and 2.2 g of benzyl chloride in 35 ml of absolute ether) contained in a three-necked flask, fitted with a reflux condenser, stirrer, and a dropping funnel. The mixture was refluxed for 5 hr and then decomposed with 2 N hydrochloric acid solution. The obtained precipitate of the bis-hydrochloride of (IV) was separated, dissolved in alcohol, and the product was precipitated by the addition of absolute ether. We obtained 1.54 g (90%) of a finely crystalline white powder, m.p. 230-231°.

Found %: N 4.52, 4.73. $C_{34}H_{36}ON_2Cl_2$. Calculated %: N 5.00.

* 2,5-Bis(benzylazomethine)furan (IId) was obtained as white crystals.

Constants and Yields of Obtained Bis-Azomethine Compounds of Furan Series

2,5-furandicarboxaldehyde (g)	Reaction components: amine, R – NH_2: R	total, g	alcohol (ml)	2,5-Bis(N-R-azomethine)furan (II): R	B.p. (0.5 mm) $n^{20}D$	M. p.	yield: in g	yield: in %	Empirical formula	% C: found	% C: calculated	% H: found	% H: calculated
1.0	CH_3	1.0	15	Methyl	80—81°	90—91° *	0.74	55	$C_8H_{10}ON_2$	64.39, 64.46	64.00	6.75, 6.92	7.19**
1.0	C_2H_5	1.6	15	Ethyl	92—93 1.5215	—	1.2	86	$C_{10}H_{14}ON_2$	66.32, 66.46	67.39	7.88, 8.02	7.92
2.0	n.-C_4H_9	3.0	30	n-Butyl	113—114 1.5340	—	2.0	54	$C_{14}H_{22}ON_2$	71.41	71.76	9.65	9.46
0.15	$C_6H_5CH_2$	0.26	3	Benzyl	—	110—111 *	0.3	83	$C_{20}H_{18}ON_2$	79.70, 79.88	79.45	6.20, 6.21	6.00
0.5	$CH_2—C_4H_3O$	0.8	10	Furfuryl	—	74—75 *	1.0	91	$C_{16}H_{14}O_3N_2$	68.23, 68.29	68.06	5.22, 5.26	4.98
1.0	C_6H_5	1.5	—	Phenyl	—	159—160 ***	2.2	Quantitative	—	—	—	—	—
0.7	o-$CH_3C_6H_4$	1.2	—	o-Tolyl	—	77—78 ****	1.4	82	$C_{20}H_{18}ON_2$	79.35, 79.38	79.45	6.13, 6.31	6.00
0.7	n-$CH_3C_6H_4$	1.2	15	p-Tolyl	—	170—171 *****	1.5	88	$C_{20}H_{18}ON_2$	79.81, 80.01	79.45	6.18, 6.30	6.00
0.5	β-$C_{10}H_7$	1.2	7	β-Naphthyl	—	230—231 ******	1.5	Quantitative	—	—	—	—	—

* From absolute ether.

** Found %: N 18.35, 18.51. Calculated %: N 18.65.

*** From absolute alcohol; literature data: m.p. 160° [2].

**** From methyl alcohol.

***** From acetonitrile. Found %: N 9.14, 9.31. Calculated %: N 9.27.

****** Literature data: m.p. 230° [2].

2,5-Bis(α-ethylamino-β,β-dicarboxyethyl)furan (V). A solution of 0.36 g of (IIb) and 0.4 g of malonic acid in 20 ml of alcohol was heated on the water bath for 10 min at 40-45° and then cooled strongly. The obtained yellow precipitate, insoluble in the common organic solvents, was purified by a double refluxing in acetone; the compound gives a positive ninhydrin reaction. We obtained 0.53 g (92%) of product, m.p. 190-191°.

Found %: C 49.78, 49.96; H 5.83, 5.99; N 6.94, 7.08. $C_{16}H_{22}O_9N_2$. Calculated %: C 49.72; H 5.74; N 7.25.

2,5-Bis(β-cyano-β-carbamoylvinyl)furan (VI). Analogous to the preparation of (V), from 0.18 g of (IIb) and 0.15 g of cyanoacetamide we obtained 0.2 g (72%) of product, m.p. 297-298° (from glacial acetic acid). The mixed melting point with (VI), obtained by a different procedure [1], was not depressed.

Bis-phenylhydrazone of 2,5-furandicarboxaldehyde (VII). a) A solution of 0.2 g of (IIc) and 0.17 g of phenylhydrazine in 10 ml of alcohol was heated to the boil and then cooled. The precipitate (VII) was separated and recrystallized from a mixture of benzene and methyl alcohol. We obtained 0.22 g (85%) of product, m.p. 206-207°.

b) From 0.2 g (IId) and 0.14 g of phenylhydrazine we obtained 0.17 g (85%) of product, m.p. 206-207° [1, 2].

c) From 0.2 g of (IIf) and 0.15 g of phenylhydrazine we obtained 0.18 g (90%) of product, m.p. 206-207°.

The mixed melting point of each preparation with (VII), obtained by a different procedure [1], was not depressed.

Reaction of 2,5-bis(N-ethylazomethine)furan (IIb) with picric acid. A solution of 0.5 g of (IIb) in 5 ml of absolute ether was added dropwise to a saturated solution of 1.3 g of picric acid in absolute ether. A yellow precipitate deposited immediately. The mixture was stirred for 30 min and then the crystals were separated. We obtained 1.5 (97%) of ethylamine picrate, m.p. 168-169° (from ethyl alcohol). Literature data: m.p. 170° [4].

Found %: C 34.93, 35.10; H 3.73, 3.79. $C_8H_{10}O_7N_4$. Calculated %: C 35.04; H 3.71.

From the filtrate after distilling off the ether we isolated 0.1 g (30%) of 2,5-furandicarboxaldehyde (I), m.p. 108-109° (from carbon tetrachloride). The mixed melting point with authentic 2,5-furandicarboxaldehyde was not depressed.

SUMMARY

1. 2,5-Furandicarboxaldehyde condenses readily with aliphatic and aromatic amines to give the corresponding bis-azomethine compounds of the furan series in good yields; the hydrogenation of the latter leads to obtaining 2,5-bis(alkylaminomethyl)furans.

2. Reaction of the bis-azomethine compounds of the furan series with Grignard reagent and with malonic acid leads to the respective formation of symmetrical secondary diamines and bis-amino acids of the furan series.

3. When reacted with cyanoacetamide and with phenylhydrazine, bis-azomethine compounds of the furan series exchange their alkyl- or arylimino group. Unstable picrates are formed when the bis-azomethine compounds are reacted with picric acid, which are easily hydrolyzed to give the picrate of the primary amine and 2,5-furandicarboxaldehyde.

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DERIVATIVES OF 7-AZAINDOLE

II. SYNTHESIS OF 1-SUBSTITUTED DERIVATIVES OF 4-METHYL-7-AZAINDOLINE WHEN 2-CHLORO-3-(β-CHLOROETHYL)-4-METHYLPYRIDINE IS REACTED WITH SECONDARY AMINES

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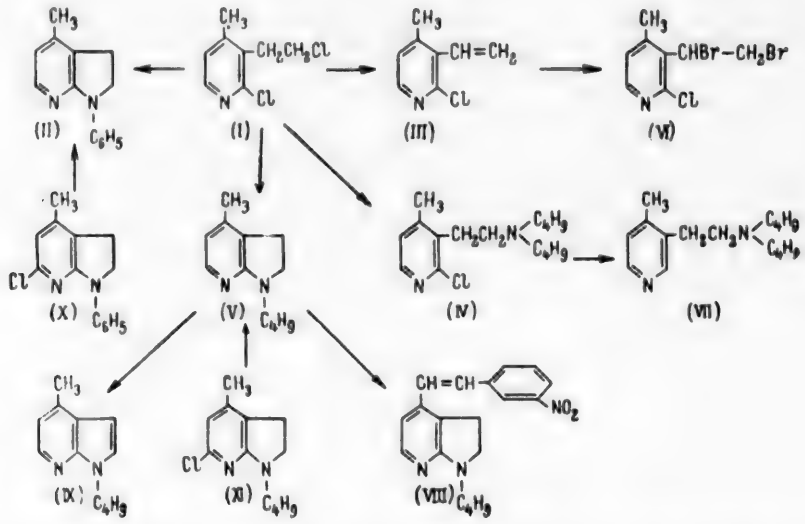
In the previous paper [1] we described a new type of closure of the pyrroline ring when 2,6 dichloro-3-(β-chloroethyl)-4-methylpyridine (trichlorocollidine) is reacted with various aliphatic and aliphatic-aromatic secondary amines, and we also established the effect exerted by the character of the substituents on the nitrogen of the secondary amine on the yield of the formed 7-azaindoline derivative.

The present paper is devoted to a study of the reaction of 2-chloro-3-(β-chloroethyl)-4-methylpyridine (I) [2] with secondary amines. The secondary amines taken for reaction were N-methylaniline, which gave the highest yield of the 7-azaindoline derivative (91%) when reacted with trichlorocollidine, and dibutylamine, which, in the case of reaction with trichlorocollidine, gave the lowest yield of the 7-azaindoline derivative (17%) and the highest number of secondary reaction products [1].



When (I) was reacted with N-methylaniline, the same as in the case of trichlorocollidine, the reaction went in a quite well-defined manner. 1-Phenyl-4-methyl-7-azaindoline (II) was obtained in 90% yield. The use of dibutylamine as the secondary amine, the same as in the case of reaction with trichlorocollidine, led to obtaining a mixture of products. Together with 1-butyl-4-methyl-7-azaindoline (V), isolated in 14% yield, we observed the formation of 2-chloro-3-vinyl-4-methylpyridine (III), and also the product of replacing one of the halogen atoms in (I) by the dibutylamine radical (IV). To isolate (IV) from the reaction mixture we used the technique of fractional distillation in vacuo, while to separate (I), (III) and (V) we capitalized on the different solubility of their hydrochlorides in acetone and ethyl acetate, and also on the ability of (III) to be converted to a higher boiling dibromo derivative (VI).

The structure of 1-phenyl-4-methyl-7-azaindoline (II) and of 1-butyl-4-methyl-7-azaindoline (V) was confirmed by their identification with the compounds formed by the dehalogenation of 1-phenyl-4-methyl-6-chloro-7-azaindoline (X) and 1-butyl-4-methyl-6-chloro-7-azaindoline (XI), respectively, which had been synthesized previously [1], while the structure of 1-phenyl-4-methyl-7-azaindoline (II) was also proved by its identification with the (II), obtained from the reaction of (I) with aniline.

To confirm the structure of 2-chloro-3-vinyl-4-methylpyridine (III), the latter was obtained pure in 98% yield by treating (I) with alcoholic NaOH, followed by conversion to the dibromo derivative (VI). The obtained dibromo derivative (VI) proved to be identical with the compound isolated from the bromination of the products obtained in the reaction of (I) with dibutylamine.

The formation of the dibutylaminochlorocollidine (IV) proved to be somewhat unexpected. As we had shown previously [1], in the reaction of trichlorocollidine with dibutylamine the product formed by replacing one of the chlorine atoms in trichlorocollidine by the dibutylamine radical still contains the β-chloroethyl group and is formed as the result of the dibutylamine radical replacing the chlorine atom in the pyridine ring, and not in the side chain. By analogy it was natural to assume that the (IV) formed in the reaction of (I) with dibutylamine is also the product of replacing the halogen atom in the ring of (I), and not in the side chain, by the dibutylamine radical, i.e., that (IV) has the structure of 2-dibutylamino-3-(β-chloroethyl)-4-methylpyridine. However, a study of the properties of (IV) disclosed the error of such an assumption. (IV) could not be converted to the corresponding vinyl derivative when treated with alcoholic NaOH solution. At the same (IV) readily underwent dehalogenation in the presence of palladium catalyst to yield a halogen-free compound. On the basis of the indicated reactions, (IV) is not 2-dibutylamino-3-(β-chloroethyl)-4-methylpyridine, but instead is 2-chloro-3-(β-butylaminoethyl)-4-methylpyridine. The halogenation product of (IV) has the structure of 3-(β-dibutylaminoethyl)-4-methylpyridine (VII).

As a result, in the case of 2-chloro-3-(β-chloroethyl)-4-methylpyridine (I) the reaction with secondary amines goes mainly in the same manner as when reaction is with trichlorocollidine. Consequently closure of the pyrroline ring with the formation of 7-azaindoline derivatives was also observed in this case, the same rules regarding the effect exerted by the character of the substituents on the secondary nitrogen atom on the ease of closure of the pyrroline ring were manifested, and the principal secondary processes in the reaction were again dehalogenation and replacement of one chlorine atom by the dibutylamine radical.

Together with this, in going from the 2,6-dichloro derivative of the pyridine to the analogous compound, but not containing halogen in the 6-position, a difference was observed relative to the manner in which the halogen atom was replaced by the dibutylamine radical. Whereas for the 2,6-dichloro derivative (trichlorocollidine) the dibutylamine radical replaced only the halogen in the nucleus, in the case of the corresponding (I), not containing halogen in the 6-position, a replacement of only the halogen atom in the side chain by the dibutylamine radical was observed.

As is known [3], 2,6-dichloropyridine derivatives exhibit certain peculiarities in chemical reactions, associated with the presence of halogen atoms in the α-position of the pyridine ring. A comparative study of the chemical properties of 6-chloro derivatives of 7-azaindoline and the corresponding dehalogenated derivatives enabled us to establish some new facts regarding the influence of halogen atoms in the α-position of the pyridine ring on the chemical properties of the compound as a whole. Thus, for example, when 1-butyl-4-methyl-7-azaindoline (V) is dehydrogenated with chloranil in boiling xylene [4] it is converted smoothly to 1-butyl-4-methyl-7-azaindole (IX). At the same time, the analogous 6-chloro derivative (XI), under the same dehydrogenation conditions, fails to react and is recovered unchanged.

The methyl group in the 4-position of 1-butyl-4-methyl-7-azaindoline (V), the same as γ-methyl group in the pyridine ring, is capable of condensing with m-nitrobenzaldehyde to yield the corresponding styryl derivative (VIII). However, the presence of the pyrroline ring in (V), condensed in the α, β-position with the pyridine ring, inhibits this reaction. The yield of the styryl derivative (VIII) is 26%, whereas when 4-methylpyridine is condensed with m-nitrobenzaldehyde under the same conditions the reaction product, m-nitrostilbazole, can be isolated in 73% yield. Introduction of a chlorine atom in the 6-position of the 7-azaindoline ring completely inactivates the methyl group in the 4-position; when (XI) is heated with m-nitrobenzaldehyde the recovery of unchanged (XI) is practically quantitative.

As a result, in the case of 7-azaindoline derivatives the introduction of chlorine in the 6-position inactivates the methyl group in the 4-position and suppresses the ability of the compound to undergo dehydrogenation in the 2,3-position.

EXPERIMENTAL

Reaction of 2-chloro-3-(β-chloroethyl)-4-methylpyridine with N-methylaniline. A mixture of 3.5 g of 2-chloro-3-(β-chloroethyl)-4-methylpyridine and 4 g of N-methylaniline was heated for 8 hr at 190°. Then the reaction mass was cooled, 15 ml of 50% potassium carbonate solution was added, and the product was extracted with benzene. The benzene solution was dried over fused potassium carbonate, filtered, and the filtrate was evaporated on the boiling water bath at a residual pressure of 5 mm. The residue distilled at 179-180° (1.3 mm). The distilled material crystallized. We obtained 3.5 g (90%) of 1-phenyl-4-methyl-7-azaindoline.

Colorless needles, m.p. 102-103° (from methanol). The substance is readily soluble in chloroform and benzene, less readily soluble in alcohols and in acetone, and is insoluble in ether, petroleum ether, and water.

Found %: C 79.97, 79.87; H 6.75, 6.77; N 13.49. $C_{14}H_{14}N_2$. Calculated %: C 80.00; H 6.66; N 13.33.

The hydrochloride was obtained as colorless crystals, m.p. 216-217°. The substance is readily soluble in chloroform and the alcohols, difficultly soluble in acetone and in dioxane, and is insoluble in ether, benzene, and ethyl acetate.

Found %: C 67.87, 68.08; H 6.12, 6.00; N 11.21, 11.48; Cl' 14.17. $C_{14}H_{14}N_2 \cdot HCl$. Calculated %: C 68.15; H 6.08; N 11.36; Cl' 14.41.

1-Phenyl-4-methyl-7-azaindoline (II). 1) To a solution of 0.25 g of 1-phenyl-4-methyl-6-chloro-7-azaindoline in 10 ml of alcohol was added 0.1 g of palladium chloride, dissolved in 1 ml of boiling 18% hydrochloric acid solution. The hydrogenation was run at a hydrogen pressure of 20-30 cm of water. The catalyst was filtered. The alcohol solution was evaporated in vacuo. We obtained 0.24 g (96%) of the hydrochloride of 1-phenyl-4-methyl-7-azaindoline. M.p. 216-217° (from dioxane). The mixed melting point with the hydrochloride of (II), obtained from the reaction of 2-chloro-3-(β-chloroethyl)-4-methylpyridine with N-methylaniline, was not depressed.

Found %: Cl 14.30; Cl' 14.70. $C_{14}H_{14}N_2 \cdot HCl$. Calculated %: Cl 14.41.

2) A mixture of 2.4 g of 2-chloro-3-(β-chloroethyl)-4-methylpyridine and 2.34 g of aniline was heated for 7 hr at 190°. The reaction was accompanied by the sublimation of aniline hydrochloride (1.3 g sublimed, m.p. 197-198°). The intensely dark reaction mass was treated with 20 ml of chloroform. The chloroform solution was filtered to remove a small amount of insoluble aniline hydrochloride, after which it was extracted with 20 ml of 50% potassium carbonate solution, and then dried over potassium carbonate. The chloroform was vacuum-distilled. The residue was recrystallized from methanol. We obtained 2.2 g (83%) of (II), m.p. 102-103°. The melting point was not depressed when the substance was mixed with the (II) obtained from the reaction of 2-chloro-3-(β-chloroethyl)-4-methylpyridine with N-methylaniline.

Reaction of 2-chloro-3-(β-chloroethyl)-4-methylpyridine with dibutylamine. A mixture of 4.9 g of 2-chloro-3-(β-chloroethyl)-4-methylpyridine and 6.3 g of dibutylamine was heated for 8 hr at 140°. Then the reaction mass was cooled and treated with 20 ml of ether and 10 ml of water. The ether solution was separated, washed with another 10 ml of water. The ether solution was separated, washed with another 10 ml of water, and dried over fused potassium carbonate. The ether was removed by distillation, while the residue was vacuum-distilled at a residual pressure of 0.4 mm. The following fractions were collected: 1st, b.p. 88-98°, 3.7 g; 2nd, b.p. 138-140°, 1.3 g. Based on the elemental analysis and chemical properties, the 2nd fraction was 2-chloro-3-(β-dibutylaminoethyl)-4-methylpyridine (IV). Yield 18%. The compound was obtained as an oily colorless substance, readily soluble in the common organic solvents, and difficultly soluble in water. $n^{20}D$ 1.5044. The substance does not cleave hydrogen chloride when refluxed with alcoholic NaOH solution, but it does undergo dehalogenation when hydrogenated in the presence of palladium catalyst.

Found %: C 67.59; H 9.26; N 10.12; Cl 12.78. $C_{16}H_{27}N_2Cl$. Calculated %: C 67.96; H 9.56; N 9.91; Cl 12.56.

The 1st fraction (3.7 g) represented a mixture of compounds, which could not be separated into individual compounds by fractional distillation in vacuo.

To separate the obtained mixture of compounds we capitalized on the difference in the solubility of their hydrochlorides in acetone and ethyl acetate. For this purpose, 3.7 g of the fraction with b.p. 88-98° (0.4 mm) was dissolved in 20 ml of ethyl acetate and then an alcoholic solution of hydrogen chloride was added until acid to Congo. A precipitate separated here, which was filtered from the ethyl acetate solution (solution A) and recrystallized from acetone. We obtained 1.5 g (16%) of the hydrochloride of 2-chloro-3-(β-chloroethyl)-4-methylpyridine. Colorless

crystals, m.p. 103-104°. The substance is readily soluble in water, alcohol and chloroform, difficultly soluble in acetone and benzene, and insoluble in ether, ethyl acetate, and toluene.

Found %: C 42.55; H 4.46; N 6.18, 6.31; Cl 47.37, 47.20. $C_8H_9NCl_2 \cdot HCl$. Calculated %: C 42.38; H 4.47; N 6.18; Cl 47.02.

The acetone solution from the removal of the hydrochloride of 2-chloro-3-(β-chloroethyl)-4-methylpyridine was evaporated in vacuo. The residue was digested with 15 ml of boiling ethyl acetate. The hot ethyl acetate solution was decanted from the insoluble oily residue. The ethyl acetate solution on cooling deposited white crystals of the hydrochloride of 1-butyl-4-methyl-7-azaindoline. Yield 0.8 g (14%). M.p. 158-159°. The substance is soluble in water, alcohol, acetone, and chloroform, less readily soluble in benzene, and insoluble in ether and ethyl acetate. The mixed melting point with the hydrochloride of (V), obtained by the dehalogenation of 1-butyl-4-methyl-6-chloro-7-azaindoline, was not depressed.

Found %: C 63.82; H 8.31; N 12.25; Cl 15.95. $C_{12}H_{18}N_2 \cdot HCl$. Calculated %: C 63.58; H 8.39; N 12.36; Cl 15.67.

The ethyl acetate solution from the removal of the mixed hydrochlorides of (I) and (V) (solution A) was washed with 15% sodium carbonate solution. After removal of the ethyl acetate in vacuo, the residue was distilled at a residual pressure of 0.4 mm, b.p. 88-90°. We obtained 1.2 g of an oily product, which proved to be readily soluble in the common organic solvents and insoluble in water. When reacted with potassium permanganate and with bromine the substance gives a positive test for the double bond. From the elemental analysis data and the properties, the material represents a mixture of approximately equal amounts of 2-chloro-3-(β-chloroethyl)-4-methylpyridine (I) and 2-chloro-3-vinyl-4-methylpyridine (III).

In view of the fact that (I) and (III) could not be separated either by fractional distillation in vacuo or by the difference in the solubility of their salts, the obtained mixture of (I) and (III) was treated with bromine, followed by separation of the 2-chloro-3-(β-chloroethyl)-4-methylpyridine (I) and 2-chloro-3-(α,β-dibromoethyl)-4-methylpyridine by fractional distillation in vacuo.

To 1 g of mixed (I) and (III) in 10 ml of anhydrous chloroform was added 0.55 g of bromine in 5 ml of anhydrous chloroform. The reaction mass became colorless. The chloroform was vacuum-distilled and the residue was subjected to fractional distillation. The following fractions were collected: 1st, b.p. 88-90° (0.4 mm), 0.4 g (8%), $n^{20}D$ 1.5535 [2] – 2-chloro-3-(q-chloroethyl)-4-methylpyridine; 2nd, b.p. 138-140° (0.4 mm), 0.9 g (11%). The 2nd fraction crystallized when rubbed with ether. Pale yellow crystals, m.p. 128°. The melting point is not depressed when the substance is mixed with the (VI) obtained by the bromination of pure 2-chloro-3-vinyl-4-methylpyridine (III).

1-Butyl-4-methyl-7-azaindoline (V). To 0.45 g of 1-butyl-4-methyl-6-chloro-7-azaindoline in 25 ml of an alcohol solution of hydrogen chloride was added 0.3 g of palladium chloride. The hydrogenation was run at room temperature and a pressure of 15-20 cm of water. Fifty milliliters of hydrogen was absorbed in 1 hr. The catalyst was filtered and the filtrate was evaporated in vacuo. We obtained 0.45 g (100% yield) of 1-butyl-4-methyl-7-azaindoline hydrochloride. M.p. 158-159°.

Found %: C 63.47; H 8.49; N 12.37; Cl' 15.80. $C_{12}H_{18}N_2 \cdot HCl$. Calculated %: C 63.58; H 8.39; N 12.36; Cl' 15.67.

The free base was obtained as a colorless oily substance with a pleasant, aromatic amine odor, b.p. 91° (1.5 mm), $n^{20}D$ 1.5329. The compound is readily soluble in organic solvents and difficultly soluble in water.

Found %: C 75.93, 75.65; H 9.50, 9.49; N 14.87. $C_{12}H_{18}N_2$. Calculated %: C 75.78; H 9.47; N 14.73.

2-Chloro-3-vinyl-4-methylpyridine (III). 2-Chloro-3-(β-chloroethyl)-4-methylpyridine (0.7 g) was refluxed with a solution of 0.15 g of NaOH in 5 ml of anhydrous alcohol for 3 hr. The precipitation of sodium chloride occurred during the reaction. The reaction mass was evaporated in vacuo. The residue was treated with 5 ml of water and then extracted with ether. The ether solution was dried over potassium carbonate, the ether was removed by distillation, and the substance (III) was vacuum-distilled. B.p. 89° (6 mm), $n^{20}D$ 1.5584. Yield 0.5 g (98%).

The compound was a colorless oily substance, readily soluble in the common organic solvents, and difficultly soluble in water.

Found %: C 62.46, 62.41; H 5.24, 5.34; N 8.98; Cl 22.97, 22.36. C_8H_8NCl. Calculated %: C 62.54; H 5.21; N 9.12; Cl 23.12.

2-Chloro-3-(α, β-dibromoethyl)-4-methylpyridine (VI). A solution of 0.2 g of (III) in 5 ml of anhydrous chloroform was treated with 0.2 g of bromine. The solution became colorless, and pale yellow crystals of (VI) deposited from it on standing. Weight 0.06 g, m.p. 128°. Removal of the chloroform left a pale yellow viscous mass, which crystallized when rubbed with ether. The total yield of (VI) was 0.37 g (90%). Pale yellow crystals, m.p. 128°, b.p. 142° (0.6 mm). The substance is readily soluble in alcohols, less readily soluble in chloroform, difficultly soluble in ether, and insoluble in water.

Found %: C 30.77; H 2.76; N 4.23, 4.36. $C_8H_8NClBr_2$. Calculated %: C 30.62; H 2.56; N 4.46.

3-(β-Dibutylaminoethyl)-4-methylpyridine (VII). A solution of 0.5 g of 2-chloro-3-(β-dibutylaminoethyl)-4-methylpyridine in 5 ml of alcohol was hydrogenated in the presence of palladium catalyst at room temperature and a water pressure of 15-20 cm. The catalyst was filtered, and the filtrate was evaporated in vacuo. The residue was treated with 5 ml of 50% potassium carbonate solution and then extracted with ether. The ether solution was dried over fused potassium carbonate. The ether was removed by distillation and the substance was vacuum-distilled. B.p. 109-110° (2 mm), $n^{20}D$ 1.4915. Yield 0.38 g (86%).

The compound is a colorless oily liquid. It is readily soluble in the common organic solvents and difficultly soluble in water.

Found %: C 77.84, 77.53; H 11.10, 11.06; N 10.92. $C_{16}H_{28}N_2$. Calculated %: C 77.42; N 11.29; N 11.29.

1-Butyl-4-methyl-7-azaindole (IX). A mixture of 1.8 g of 1-butyl-4-methyl-7-azaindoline, 2 g of chloranil and 20 ml of anhydrous xylene was refluxed for 1.5 hr. The xylene layer was decanted from the tarry precipitate, extracted 4 times with 10 ml of portions of 10% aqueous KOH solution, washed with water, and dried over fused potassium carbonate. The xylene was removed by distillation and the residue was vacuum-distilled. B.p. 91° (0. 8 mm), $n^{20}D$ 1.5513. We obtained 0.8 g (45%) of 1-butyl-4-methyl-7-azaindole (IX). The compound was obtained as a pale yellow oily liquid. It is readily soluble in the common organic solvents and difficultly soluble in water.

Found %: C 76.20, 76.23; H 8.39, 8.22; N 14.64, 14.58. $C_{12}H_{16}N_2$. Calculated %: C 76.59; H 8.51; N 14.89.

1-Butyl-4-(m-nitrostyryl)-7-azaindoline (VIII). A mixture of 2.05 g of 1-butyl-4-methyl-7-azaindoline and 2 g of m-nitrobenzaldehyde in 10 ml of acetic anhydride was heated for 6 hr on the boiling water bath. The obtained solution was evaporated in vacuo. The residue was treated with 15 ml of a 10% hydrochloric acid solution and the resulting solution was extracted with benzene. Then the aqueous acid solution was treated with 50% potassium carbonate solution until alkaline to phenolphthalein, followed by extraction with chloroform. The chloroform extract was dried over fused potassium carbonate and then evaporated in vacuo. The residue from the removal of the chloroform was treated with 30 ml of ether. A crystalline precipitate was obtained. Yield 0.9 g (26%). Pale yellow crystals, m.p. 146-147° (from benzene). The substance is readily soluble in alcohols, less readily soluble in chloroform, and insoluble in water, ether, acetone, and benzene.

Found %: C 70.48; H 6.52; N 12.89. $C_{19}H_{21}O_2N_3$. Calculated %: C 70.59; H 6.50; N 13.00.

The ether solution from the removal of (VIII) was evaporated in vacuo. The residue was vacuum-distilled. We obtained 1 g (48.8%) of 1-butyl-4-methyl-7-azaindoline, b.p. 91° (1.5 mm), $n^{20}D$ 1.5330.

The condensation of m-nitrobenzaldehyde with 4-methylpyridine under the same conditions gave 3-nitrostilbazole in 73% yield, m.p. 139-140° [5], while when m-nitrobenzaldehyde is condensed with 1-butyl-4-methyl-6-chloro-7-azaindoline the starting compounds are recovered unchanged.

SUMMARY

1. The synthesis of 1-substituted derivatives of 4-methyl-7-azaindoline was accomplished by reacting 2-chloro-3-(β-chloroethyl)-4-methylpyridine with secondary amines.

2. It was shown that when secondary amines are reacted with 2-chloro-3-(β-chloroethyl)-4-methylpyridine the same rules hold for the influence exerted by the character of the substituents on the secondary nitrogen atom on the ease of closure of the pyrroline ring as when secondary amines are reacted with trichlorocollidine.

3. It was established that introduction of the chlorine atom in the 6-position of 7-azaindoline derivatives inactivates the methyl group in the 4-position and suppresses the ability of the compound to undergo dehydrogenation in the 2,3-position.

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β-AMINO ACIDS OF THE THIANAPHTHENE SERIES

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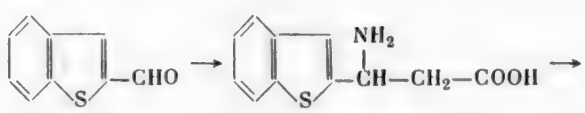
The thianaphthene analog of tryptophan – β-(3-thianaphthenyl)-α-alanine is an effective antagonist for tryptophan [1], and also an inhibitor for the growth of certain streptococci [2]. Since it is known that in a number of cases β-amino acids posses biological activity [3], it seemed of interest to prepare some β-amino acids of the thianaphthene series and test them as tryptophan antagonists.

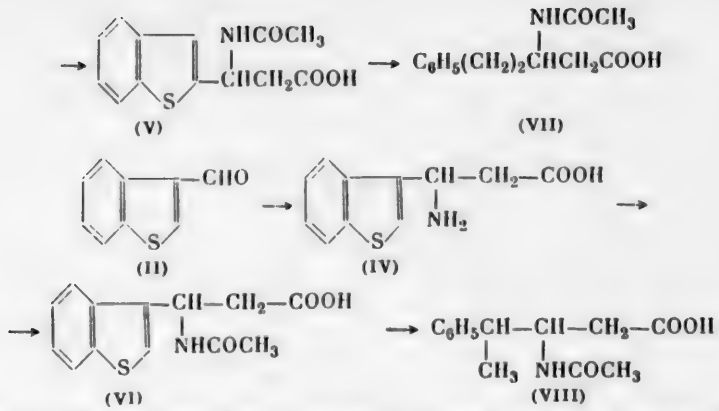
It is known that the simplest and most convenient procedure for the synthesis of β-amino acids is the V. M. Rodionov method, involving the reaction of an aldehyde with amlonic acid and ammonia. In the present study we used 2-thianaphthenecarboxaldehyde (I) [4] and 3-thianaphthenecarboxaldehyde (II) [5] to prepare the corresponding β-amino acids. By modifying the method of preparation we were able to raise the yield of 2-thianaphthenecarboxaldehyde from 62 to 77%. Using the Rodionov method, β-(2-thianaphthenyl)-β-alanine (III) and β-(3-thianaphthenyl)-β-alanine (IV) were synthesized in yields of 66.5 and 55.8%, respectively. The ratio of the reactants and the reaction temperature were analogous to those used previously in the synthesis of β-(2-thienyl)-β-alanine [6]. Using paper chromatography [7], it was established that in the case of 2-thianaphthenecarboxaldehyde the reaction is ended in 40-50 min, while 3-thianaphthenecarboxaldehyde requires 3-3.5 hr for complete reaction. It is interesting to mention that if the condensation with 2-thianaphthenecarboxaldehyde went much faster than with 3-thianaphth enecarboxaldehyde, then, in contrast, 2-thiophenecarboxaldehyde reacted more slowly than did 3-thiophenecarboxaldehyde [8]. This observation is in harmony with the statements found in the literature that a certain analogy exists in the reactivity of the 2-position in thiophene and the 3-position in thianaphthene [9].

To isolate the thianaphthene β-amino acids from the reaction mixture they were first converted to the hydrochlorides, and then the free β-amino acids were obtained on analytically pure form by using the ion-exchange resin "Dowex 50W X-4." Both β-(2-thianaphthenyl)-β-alanine and β-(3-thianaphthenyl)-β-alanine were obtained as colorless, very fine flat prisms, difficultly soluble in water, and readily soluble in aqueous acetic acid, dilute hydrochloric acid, and potassium bicarbonate solution. To characterize the new β-amino acids we prepared their acetyl and benzoyl derivatives. Besides the β-amino acids, we also isolated β-(2-thianaphthenyl)acrylic and β-(3-thianaphthenyl)acrylic acids from the respective reaction mixtures.

We also ran some experiments on the reductive desulfurization of the synthesized thianaphthene β-aminoacids using Raney nickel for the purpose of determining if arylaliphatic β-amino acids could be obtained from the thianaphthene derivatives. As is known, thiophene derivatives, including the β-amino acids [10], are readily amenable to this type of desulfurization, which makes it possible to obtain various aliphatic compounds from them [11]. Analogous reactions for thianaphthene derivatives have received much less study, although in a number of cases it has been stated that the reaction goes with high yields [12-15]. We subjected the N-acetyl derivatives of the thianaphthenyl-β-alanines to desulfurization, since it was shown by Gol'dfarb and coworkers [10] that the desulfurization of thiophene β-amino acids goes more smoothly when the N-acetyl derivatives are used. Actually, we found that the N-acetylamino acids (V) and (VI) are desulfurized with ease to give N-acetyl-δ-phenyl-β-aminovaleric (VII) and N-acetyl-γ-phenyl-β-aminovaleric (VIII) acids, respectively, whereas the free β-amino acids under analogous conditions gave unsatisfactory results.



(I) (III)



The testing of the two β-thianaphthenyl-β-alanines on a strain of B. coli deficient in tryptophan was done by Z. I. Bandur and E. I. Voronina, coworkers at the Institute of Cytology and Genetics of the Siberian Section of the Academy of Sciences of the USSR. It was shown by them that both β-amino acids are incapable of serving as tryptophan substitutes and are not antagonists for it.

EXPERIMENTAL

2-Thianaphthenecarboxaldehyde (I) was prepared by a modification of the method given in [4]. A solution of 18 g of butyl bromide in 24 ml of absolute ether was added gradually, with stirring, to 2.4 g of finely cut lithium in 40 ml of absolute ether. The mixture was cooled with water in such manner that the temperature remained at a gentle ether boil, after which it was stirred for another hour at 18°, and then filtered rapidly through glass wool. Then with cold water cooling, a solution of 10.8 g of thianaphthene in 25 ml of absolute ether was added in drops, with stirring, to the filtrate, after which the mixture was stirred for 1.5 hr at 18°. This was followed by the dropwise addition of a solution of 10.8 g of N-methylformanilide in 16 ml of absolute ether, after which the mixture was stirred, allowed to stand overnight, and then poured into a mixture of 42 ml of 3 N hydrochloric acid and ice. The ether layer was separated, and the water layer was extracted 3 times with ether. The combined ether extracts were washed with 1 N hydrochloric acid, then with 10% sodium bicarbonate solution, next with water, and dried over anhydrous sodium sulfate. After removal of the ether by distillation the residue was dissolved in 15 ml of alcohol, 60 ml of a saturated sodium bisulfite solution was added, the whole was cooled, and the precipitate was filtered. The precipitate was washed with ether, dried, suspended in 250 ml of water, and then decomposed by the addition of saturated sodium carbonate solution. The aldehyde was filtered, washed with water, and dried in vacuo over phosphorus pentoxide. Yield 10.3 g(77%). M.p. 33.5-34.5°. Literature data: m.p. 34-34.5° [4].

3-(Chloromethyl)thianaphthene was obtained in 30% yield by the chloromethylation of thianaphthene. B.p. 138-139° at 10 mm. Literature data [1]: b.p. 129-131° (5 mm).

3-Thianaphthenecarboxaldehyde (II) was synthesized from 3-(chloromethyl)thianaphthene by the procedure given in [5]. Yield 50%, m.p. 56-57°. Literature data: m.p. 58° [5].

β-(2-Thianaphthenyl)-β-alanine (III). A mixture of 3 g of 2-thianaphthenecarboxaldehyde, 3.4 g of malonic acid and 8.4 g of ammonium acetate in 20 ml of glacial acetic acid was heated for 1 hr in an oil bath at 110°, after which the acetic acid was vacuum-distilled at 60-70°. The residue was shaken with 20 ml of 10% hydrochloric acid solution and the yellow suspension was separated by centrifuging; this operation was repeated 3 times. The hydrochloric acid solution was filtered and then passed through a column containing ion-exchange resin "Dowex 50W X-4" (the column diameter was 10 mm, and the height was 250 mm). The column was washed with water until neutral, then with acetone, and again with water. The amino acid was eluted with 2 N ammonia solution until the ninhydrin test was negative. The eluate was evaporated in vacuo to dryness at a temperature not exceeding 60°. The residue was washed with alcohol, then with ether, and dried in vacuo over phosphorus pentoxide at 100°. We obtained 2.71 g (66.5%) of analytically pure amino acid, m.p. 241-241.5° (decompn.).

Found %: C 59.76, 59.65; H 4.89, 5.01; N 6.23, 6.33. $C_{11}H_{11}O_2NS$. Calculated %: C 59.70; H 5.01; N 6.33.

β-(2-Thianaphthenyl)acrylic acid. The centrifuged residue from the preceding experiment was transferred to a filter, washed with a little water, and dried in vacuo over phosphorus pentoxide. Yield 1.02 g (27.3%), m.p. 234-235° (decompn.) (from alcohol). Literature data: m.p. 235-237° (decompn.) [13].

N-Benzoyl-β-(2-thianaphthenyl)-β-alanine was obtained by the benzoylation of (III), using the Schotten-Baumann procedure. M.p. 194-195° (from alcohol).

Found %: C 65.96, 66.08; H 4.87, 4.79; N 4.38, 4.40. $C_{18}H_{15}O_3NS$. Calculated %: C 66.44; H 4.65; N 4.30.

N-Acetyl-β-(2-thianaphthenyl)-β-alanine (V) was obtained by the acetylation of (III) with acetic anhydride in 3 N NaOH solution; the product was dried in vacuo over phosphorus pentoxide at 100°. M.p. 230.5-231.5° (from water).

Found %: N 4.90, 4.98. $C_{13}H_{13}O_3NS$. Calculated %: N 5.32.

N-Acetyl-δ-phenyl-β-aminovaleric acid (VII). With vigorous stirring and heating on the water bath, 4 g of skeletal nickel was added in portions, in 1.5 hr, to a solution of 0.19 g of (V) in 10 ml of a 10% sodium carbonate solution. Then the mixture was filtered, and the filtrate was acidified with conc. hydrochloric acid to pH 4-5 and evaporated slightly. The residue on cooling deposited a white, finely crystalline precipitate, which was filtered, washed with a little water, and dried. Yield 0.09 g (53%), m.p. 121.5-122° (from water). According to Horton and Thompson, the amino acid (VII) obtained from γ-phenyl-α-aminobutyric acid by the Arndt-Eistert method has m.p. 122-124° [14].

β-(3-Thianaphthenyl)-β-alanine (IV). A mixture of 2 g of 3-thianaphthenecarboxaldehyde, 3.4 g of malonic acid and 8.4 g of ammonium acetate in 20 ml of glacial acetic acid was heated for 4 hr in an oil bath at 110°. After working up the mixture as described for (III), we obtained 1.52 g (55.8%) of (IV), m.p. 241-242°.

Found %: C 59.54, 59.70; H 4.83, 4.82; N 6.34, 6.47. $C_{11}H_{11}O_2NS$. Calculated %: C 59.70; H 5.01; N 6.33.

β-(3-Thianaphthenyl)acrylic acid was obtained in 25% yield (0.63 g), m.p. 223-224° (decompn.) (from aqueous alcohol). Literature data: m.p. 225° [15].

N-Benzoyl-β-(3-thianaphthenyl)-β-alanine was obtained by the benzoylation of (IV), using the Schotten-Baumann method. M.p. 210-210.5° (from aqueous alcohol).

Found %: C 66.34, 66.31; H 4.90, 4.82; N 4.54, 4.37. $C_{18}H_{15}O_2NS$. Calculated %: C 66.44; H 4.65; N 4.30.

N-Acetyl-β-(3-thianaphthenyl)-β-alanine (VI) was obtained by the acetylation of (IV) with acetic anhydride in 3 N NaOH solution. M.p. 191-192° (from aqueous alcohol).

Found %: N 5.13, 4.98. $C_{13}H_{13}O_3NS$. Calculated %: N 5.32.

N-Acetyl-γ-phenyl-β-aminovaleric acid (VIII). The desulfurization of 0.15 g of (VI), as described for the synthesis of (VII), gave 0.07 g of (VIII). M.p. 141-142° (from water). The qualitative test for sulfur was negative.

Found %: N 5.88, 6.05. $C_{13}H_{17}O_3N$. Calculated %: N 5.95.

SUMMARY

1. The Rodinov method was used to synthesize β-(2-thianaphthenyl)-β-alanine and β-(3-thianaphthenyl)-β-alanine.

2. It was shown that the reductive desulfurization of the acetyl derivatives of thianaphthene β-amino acids proceeds in normal fashion, giving arylaliphatic β-acetamino acids.

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CYCLOSERINE AND RELATED COMPOUNDS

XIV. 4-AMINO-3-PYRAZOLIDONE (AZACYCLOSERINE)

N. K. Kochetkov, É. I. Budovskii, and Chang Chih-p'ing

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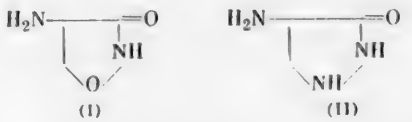
pp. 3292-3298, October, 1961
Original article submitted November 9, 1960

The synthesis of various analogs of 3-isoxazolidone, earlier realized in our laboratory, enabled the first communications on the mechanism of action of the antibiotic cycloserine (I) to be submitted [1].

In view of the need for new data on this problem, considerable interest is attached to the synthesis of analogs of cycloserine with a changed heterocyclic ring, namely 4-amino-3-pyrazolidone (II)



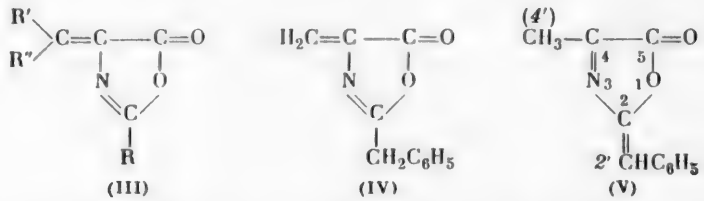
(I) (II)

In the preceding paper [2] we showed that 4-acetylamino-5-substituted 3-pyrazolidones, prepared by reaction of unsaturated azlactones (III) with hydrazine hydrate, are converted by hydrogen chloride in anhydrous methanol into dihydrochlorides of 4-amino-5-substituted 3-pyrazolidones. However the removal of the benzoyl group in similar fashion from the resulting 4-benzoylamino-3-pyrazolidone and conversion to the azacycloserine itself could not be effected.

The present communication is devoted to a study of the synthesis of 4-amino-3-pyrazolidone by another route.

It is well known that the phenacetamidino group is hydrolyzed with very much greater facility than the benzamidino group, and it was therefore to be expected that deacylation of 4-phenacetylamino-3-pyrazolidone would proceed more easily and could lead to azacycloserine.

The most convenient method of synthesis of 4-phenacetylamino-3-pyrazolidone in accordance with our observations [2] was the reaction of 2-benzyl-4-methylene-5-oxazolidone (IV) with hydrazine. Examination of the literature [3, 4] showed, however, that the sole product of the reaction is the isomeric 2-benzylidene-4-methyl-5-pseudooxazolidone (V).



(III) (IV) (V)

For this reason we made a close study of the problem of transition from the pseudooxazolone (V) to azacycloserine and in particular of the reaction of pseudooxazolones with hydrazine hydrate. It was found that, unlike what happens in the reaction with unsaturated azlactones (III), pseudooxazolones (V) reacts with hydrazine hydrate in alcohol in the cold like a 1,4-compound; the hydrazine molecule adds on in the 4,2'-position of the heterocyclic ring and gives 2-benzyl-4-hydrazino-5-oxazolone (VI). The latter subsequently undergoes ring-opening under the action of excess of hydrazine and is converted into the hydrazide of α-hydrazino-α-N-phenacetylalanine (VII). The hydrazide is hydrolyzed on treatment with hydrogen chloride in anhydrous methanol to give the dihydrochloride of the methyl ester of α-hydrazino-α-alanine (VIII). Reaction of pseudooxazolone (V) with hydrazine hydrate at a higher

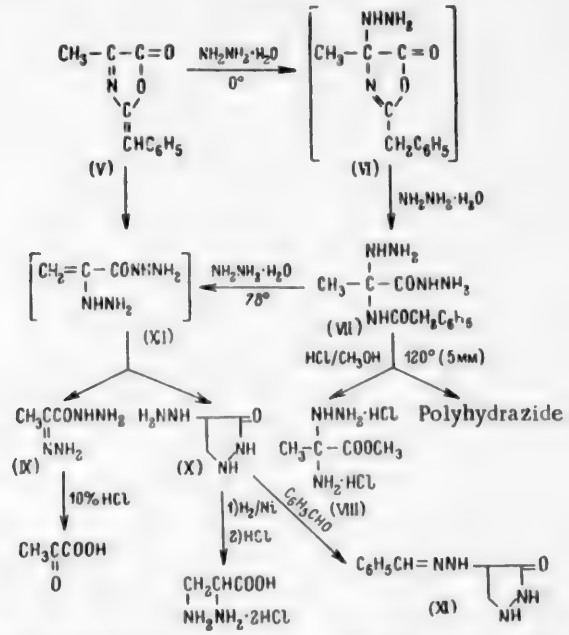
temperature gives two new compounds melting at 150-151° (IX) and 126-128° (X). The first was identical with the hydrazone of pyruvic acid hydrazide prepared from ethyl pyruvate. The second substance forms a monohydrazone (XI) with benzaldehyde. Hydrogenation over skeletal nickel [5] and subsequent hydrolysis with hydrochloric acid converts (X) into the dihyrochloride of α, β-diaminopropionic acid. The latter was identified in the form of the free aminoacid [6] by paper chromatography. Consequently (X) has the structure of 4-hydrazino-3-pyrazolidone.

The hydrazide of α-hydrazino-N-phenacetylalanine (VII) is a new type of α-substituted acid, and we investigated several of its reactions. Heating of (VII) at 120° in vacuo leads to removal of hydrazine with formation of a polyhydrazide. The latter is a yellow substance, insoluble in organic solvents and water, melting at 320° with decomposition. Heating of (VII) with an alcoholic solution of hydrazine hydrate gives a mixture of (IX) and (X). The literature [4] reports that the phenacetamidino group of α,α-diphenacetylaminopropionic acid is easily split off with formation of α-phenacetylaminoacrylic acid. The obvious inference was that in our case (IX) and (X) are probably formed via intermediate formation of α-hydrazinoacrylic acid hydrazide (XII).

Scheme 1 is a summary of all the transformations, here described, of products of reaction of pseudooxazolone (V) with hydrazine.

It follows from the foregoing data that direct opening of the ring of pseudooxazolone (V) by the action of hydrazine does not lead to the nearest analog of cycloserine – "azacycloserine" (II).

Scheme 1

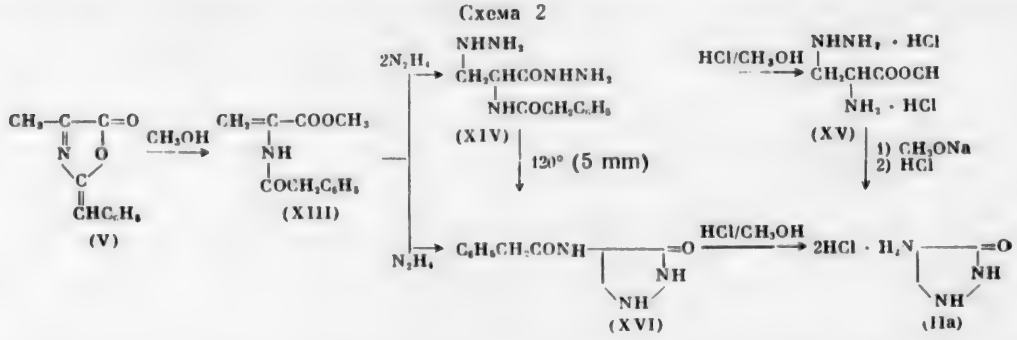


We then proceeded to study another synthesis route for (II) which involved opening of the ring of pseudooxazolone (V) by treatment with methanol. Methanolysis of pseudooxazolone (V) in presence of anhydrous potassium carbonate or sodium methoxide follows the same course as for the majority of oxazolones, namely with formation of the methyl ester of α-phenacetaminoacrylic acid (XIII). Reaction of ester (XIII) with excess of hydrazine hydrate in alcohol at room temperature gives the hydrazide of β-hydrazino-α-N-phenacetylalanine (XIV), which reacts with hydrogen chloride in anhydrous methanol to form the dihydrochloride of the methyl ester of β-hydrazino-α-alanine (XV). The latter is the analog of the ester of β-aminohydroxyalanine – the key substance for the synthesis of cycloserine [7] – and resembles it in cyclizing under the action of sodium methoxide. In the present case the product of cyclization is 4-amino-3-pyrazolidone (II).

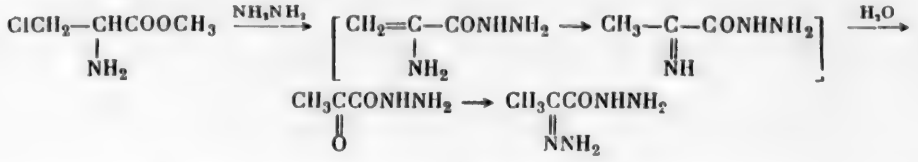
Reaction of ester (XIII) with a small excess of hydrazine hydrate in alcohol and subsequent heating gives 4-phenacetylamino-3-pyrazolidone (XVI). The latter is also formed when the hydrazide of β-hydrazino-α-N-phenacetylalanine (XIV) is heated. Deacylation of 4-phenacetylamino-3-pyrazolidone could be effected by treatment with an alcoholic solution of hydrogen chloride.

This variant consequently also leads to azacycloserine. All the transformations involved in the synthesis of azacycloserine via the methyl ester of α-phenacetylaminoacrylic acid are set forth in the over-all scheme 2.

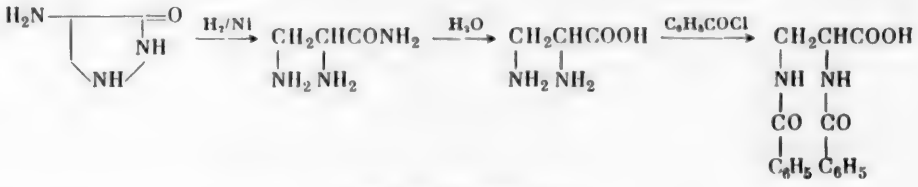
Схема 2



We also attempted to prepare azacycloserine by a simpler method – reaction of the methyl ester of β-chloroalanine with hydrazine hydrate. The result was negative: the hydrazine hydrate (as a strong base) directed the reaction towards dehydrochlorination and hydrolysis of the intermediate product – α-iminopropionic acid hydrazide. The final product was the hydrazone of pyruvic acid hydrazide.



We verified the structure of the prepared 4-amino-3-pyrazolidone by hydrogenation over skeletal nickel which gave α, β-diaminopropionamide. This was identified in the form of α, β-diaminopropionic acid [6] and its dibenzoyl derivative [8].



EXPERIMENTAL

α-Hydrazino-α-N-phenacetylalanine hydrazide (VII). Dropwise addition of 5 ml of hydrazine hydrate was made at 0-5° to a suspension of 10 g of 2-benzylidene-4-methyl-5-pseudooxazolone in 100 ml of alcohol. Stirring was continued until solution was complete. White crystals came down after 8 min. The reaction mixture was cooled with ice, and the crystals were filtered off, washed with alcohol and ether. Yield of (VII) 10 g (76%), m.p. 110-111° (from alcohol).

Found %: C 52.33, 52.33; H 6.81, 6.99; N 27.27, 27.15. $C_{11}H_{17}O_2N_5$. Calculated %: C 52.50; H 6.82; N 27.76.

Methyl ester of α-hydrazino-α-alanine dihydrochloride (VIII). To a solution of 2.5 g of α-hydrazino-α-N-phenacetylalanine hydrazide in 50 ml of absolute methanol was added 100 ml of a saturated solution of hydrogen chloride in anhydrous methanol. The temperature was held below 0° during the operation. The mass was allowed to stand for 20 min at 0° and for 2 hr at room temperature. It was then cooled to –5°, and the crystals of hydrazine dihydrochloride were filtered off. Anhydrous ether was added to the filtrate. The precipitated white substance was separated by filtration and washed with ether. The residue was dissolved in 25 ml of anhydrous methanol and again brought down with anhydrous ether. Yield of (VIII) 1 g (77%), m.p. 201-203°.

Found %: N 20.54, 20.69; Cl 34.39, 34.28. $C_4H_{11}O_2N_3 \cdot 2HCl$. Calculated %: N 20.41; Cl 34.40.

4-Hydrazino-3-pyrazolidone (X) and hydrazone of pyruvic acid hydrazide (IX). a) From pseudooxazolone (V). A mixture of 3 g of 2-benzylidene-4-methyl-5-pseudooxazolone, 4 ml of hydrazine hydrate, and 10 ml of anhydrous

alcohol was boiled for 40 min on a water bath, cooled, and left for 2 hr at 0°. The precipitated white crystals were filtered off and washed with cold alcohol and ether. Yield of mixture of (IX) and (X) 1.1 g, m.p. 124-136°. The mixture was recrystallized from 10 ml of anhydrous alcohol and 0.7 g of hydrazone of pyruvic acid hydrazide was obtained with m.p. 150-151°. No melting point depression in admixture with an authentic specimen obtained from the ester of pyruvic acid (see below).

Found %: C 31.03, 31.24; H 6.89, 6.80; N 48.12, 49.00. $C_3H_8ON_4$. Calculated %: C 31.03; H 6.89; N 48.20.

The filtrate was evaporated to dryness, and the residue recrystallized from a small quantity of a mixture of alcohol and ether. Yield 0.2 g of 4-hydrazino-3-pyrazolidone with m.p. 126-128°.

Found %: C 31.35, 31.05; H 7.06, 7.22; N 48.91, 48.76. $C_3H_8ON_4$. Calculated %: C 31.03; H 6.89; N 48.20.

b) From α-hydrazino-α-N-phenacetylalanine hydrazide. A mixture of 1.5 g of α-hydrazino-α-N-phenacetylalanine hydrazide, 1.5 ml of hydrazine hydrate, and 15 ml of anhydrous alcohol was boiled for 30 min on a water bath. The mass was worked up in the above manner to give 0.38 g of hydrazone of pyruvic acid hydrazide with m.p. 150-151° and 0.11 g of 4-hydrazino-3-pyrazolidone with m.p. 126-128°.

c) From ethyl pyruvate. A mixture of 2.31 g of ethyl pyruvate and a solution of 2 ml of hydrazine hydrate in 10 ml of anhydrous alcohol was boiled for 2 hr. After an interval of 48 hr, the crystals were filtered off. Yield of hydrazone of pyruvic acid hydrazide 1.7 g (74%), m.p. 150-151° (from alcohol).

Methyl α-phenacetylaminoacrylate (XIII). To a mixture of 3.8 g of 2-benzylidene-4-methyl-5-oxazolone in 50 ml of methanol was added a solution of sodium methoxide (from 0.24 g of sodium and 15 ml of methanol), and stirring was continued until solution was complete. The mass was evaporated to dryness, the residue dissolved in 20 ml of methanol, and 200 ml of ether added. The precipitated sodium methoxide was removed by filtration and the filtrate evaporated to dryness. The residue crystallized on standing. Yield of (XIII) 4 g (91%), m.p. 57-60°.

Found %: N 6.45, 6.64. $C_{12}H_{13}O_3N$. Calculated %: N 6.40.

β-Hydrazino- α-N-phenacetylalanine hydrazide (XIV). To a solution of 2.2 g of methyl α-phenacetylaminoacrylate in 25 ml of alcohol was added 1.25 ml of hydrazine hydrate, and the mixture was allowed to stand at room temperature. After two days the crystals were filtered off, washed with alcohol and ether. Yield 1 g. The filtrate was evaporated in vacuo to give an additional yield of 0.2 g; total yield 1.2 g (47%), m.p. 108-109° (decompn.).

Found %: C 52.29, 52.30; H 6.75, 6.77; N 27.29, 27.17. $C_{11}H_{17}O_2N_5$. Calculated %: C 52.50; H 6.82; N 27.76.

Methyl ester of β-hydrazino- α-alanine dihydrochloride (XV). To a solution of 1 g of β-hydrazino- α-N-phenacetylalanine hydrazide in 20 ml of anhydrous methanol at 0° was added 40 ml of a saturated solution of hydrogen chloride in anhydrous methanol. The mass was allowed to stand at room temperature for 4 hr and then overnight in a refrigerator (0 to –5°). The precipitated hydrazine dihydrochloride was filtered off. To the filtrate was added 200 ml of ether, and the white precipitate was filtered off, washed with ether, dissolved in 10 ml of anhydrous methanol, and again brought down with ether. Yield of dihydrochloride (XV) 0.3 g (56%), m.p. 182° (decompn.).

Found %: Cl 34.56, 34.59. $C_4H_{11}O_2N_3 \cdot 2HCl$. Calculated %: Cl 34.40.

4-Phenacetylamino-3-pyrazolidone (XVI). a) From methyl α-phenacetylaminoacrylate. A mixture of 2.2 g of methyl α-phenacetylaminoacrylate, 0.5 ml of hydrazine hydrate, and 15 ml of anhydrous methanol was allowed to stand for 1.5 hr, then boiled for 15 min, and cooled in a refrigerator at 0-5°. The precipitated crystals were filtered off and washed with ether. Yield 1.1 g (48%) m.p. 171-172° (from alcohol).

Found %: Cl 59.60; H 6.37; N 19.36, 19.35. $C_{11}H_{13}O_2N_3$. Calculated %: C 60.35; H 5.94; N 19.17.

b) From β-hydrazino-α-phenacetylalanine hydrazide. β-Hydrazino- α-phenacetylalanine hydrazide (1 g) was heated for an hour at 120° in vacuo (5 mm). The cooled product was recrystallized from alcohol. Yield 0.5 g (57%), m.p. 171-172°.

4-Amino-3-pyrazolone dihydrochloride (IIa). a) To a solution of 1 g methyl ester of β-hydrazino- α-alanine dihydrochloride in 10 ml of anhydrous methanol was added a solution of sodium methoxide (from 0.23 g of sodium and 10 ml of anhydrous methanol). The mixture was boiled for 2 hr and allowed to stand overnight. The precipitated sodium chloride was filtered off, the filtrate evaporated to dryness in vacuo, the residue dissolved in 10 ml of anhydrous methanol, and the solution filtered. To the filtrate at about –5 to –8° was added 15 ml of 40% solution of

hydrogen chloride in absolute methanol. Filtration was then followed by addition of 150 ml of ether to the filtrate. The precipitated substance was filtered. Yield 0.31 g (34%). After reprecipitation with ether from methanol, the product had m.p. 165-167°.

Found %: N 24.12, 24.22; Cl 40.02, 40.05. $C_3H_7ON_3 \cdot 2HCl$. Calculated %: N 24.12; Cl 40.05.

b) A solution of 0.5 g of 4-phenacetylamino-3-pyrazolidone in 30 ml of anhydrous methanol at 10-13° was saturated with dry hydrogen chloride and left at room temperature for 2 hr. The excess of hydrogen chloride was purged out with nitrogen, and the liquid evaporated in vacuo. The residue crystallized when triturated with ether; the crystals were dissolved in methanol and precipitated with ether. Yield 0.12 g (35%).

Reaction of 4-hydrazino-3-pyrazolidone with benzaldehyde. A mixture of 0.34 g of 4-hydrazino-3-pyrazolidone, 0.31 g of benzaldehyde, and 5 ml of methanol was boiled for an hour, the methanol was evaporated, and 20 ml of water added to the residue. After an interval of 30 min, the crystals were filtered off and recrystallized from isopropyl alcohol. Yield of hydrazone (XI) 0.25 g (42%), m.p. 159-161°.

Found %: N 25.57, 25.45. $C_{10}H_{12}ON_4 \cdot H_2O$. Calculated %: N 25.20.

Hydrogenation of 4-hydrazino-3-pyrazolidone. The pyrazolidone (0.1 g) was dissolved in anhydrous methanol (10 ml) and hydrogenated in presence of Raney nickel at room temperature. After an interval of an hour, the catalyst was filtered off and the filtrate evaporated to dryness in vacuo. The residue was boiled for 5 min with 1 ml of 10% hydrochloric acid, made alkaline, and chromatographed on paper.

R_f 0.23 (n-butyl alcohol : acetic acid : water = 3 : 3 : 5, Leningrad paper No. 2). Under the same conditions α, β-diaminopropionic acid prepared from α, β-dibromopropionic acid gives R_f 0.23 [6].

Hydrogenation of 4-amino-3-pyrazolidone. A solution of 0.1 g of 4-amino-3-pyrazolidone dihydrochloride in 10 ml of methanol was neutralized with sodium methoxide solution (from 0.07 g of sodium and 2 ml of methanol) at 0° and hydrogenated over Raney nickel. The mass was worked up as above to give a substance with R_f 0.23.

α, β-Dibenzoylaminopropionic acid. A solution of 0.5 g 4-amino-3-pyrazolidone in 15 ml of anhydrous methanol was neutralized with sodium methoxide (from 0.12 g of sodium and 10 ml of anhydrous methanol) at 0° and filtered. To the filtrate was added 1 g of Raney nickel and hydrogenation was performed at room temperature. The catalyst was filtered off after 2.5 hr, and the filtrate evaporated in vacuo. The oily residue was dissolved in 10 ml of 5% sodium hydroxide solution at 18° with prolonged stirring and benzoylated with 1 ml of benzoyl chloride. After acidification, the precipitate was washed with water and cold ether. Yield of α, β-dibenzoylaminopropionic acid 0.03 g, m.p. 205-207° (from alcohol). A mixture with a specimen prepared from α,β-diaminopropionic acid did not give a depression of melting point.

SUMMARY

1. 4-Amino-3-pyrazolidone was synthesized.

2. The action of hydrazine hydrate on 5-pseudooxazolones was investigated.

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STEREOCHEMICAL INVESTIGATIONS ON LEVOMYCETIN DERIVATIVES (CHLOROAMPHENICOLS)

I. HYDROLYSIS OF NITRO ESTERS OF THREO- AND ERYTHRO-1-(p-NITROPHENYL)-2-ACYLAMINO-1,3-PROPANEDIOLS

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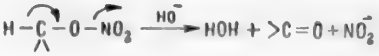
Interconversion of the diastereoisomeric threo- and erythro-1-(p-nitrophenyl)-2-acylamino-1,3-propanediols was hitherto realized by replacement of OH (at the C_1) by Cl or by formation and hydrolysis of oxazoline rings [1, 2].

We were interested in the possibility of effecting the Walden inversion at the C_1 in N-acyl derivatives of threo- and erythro-1-(p-nitrophenyl)-2-amino-1,3-propanediols by hydrolysis of their O_1,O_3-dinitro esters.

It was earlier shown in a number of cases that the process of formation of nitro esters of optically active alcohols proceeds without change of configuration, whereas in the hydrolysis of the nitro esters the change of configuration depends on the conditions employed [3, 4]. For example, the original configuration of the alcohol is largely retained in hydrolysis of (+)-2-octyl nitrate in an alkaline or acid medium (in alcoholic solution), whereas hydrolysis of the same nitro ester in a neutral medium led to inversion of the alcohol to the extent of 85% [4].

For the purpose of the planned investigation we prepared O_1,O_3-dinitro esters of DL- and L-threo-1-(p-nitrophenyl)-2-acetylamino- and 1-(p-nitrophenyl)-2-dichloroacetylamino-1,3-propanediols, and also the dinitro ester of L-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. These dinitro esters were synthesized by reaction of the corresponding diols with a mixture of concentrate nitric and sulfuric acids. The hydrolysis of the resulting nitro esters could not be carried out in alcoholic alkali or in an aqueous-alcoholic alkaline medium since heating under these conditions led to serious resinification of the reaction products. It was likewise impossible to obtain the usual product of hydrolysis when the reaction temperature was lowered to 10-15°; the substance isolated under these conditions could not be easily purified and identified. It was found that this reaction was invariably accompanied by separation of $NaNO_2$ in the proportion of about 2 moles per mole of initial dinitro ester. It was therefore plausible to assume that a concurrent reaction takes place, usually with removal of the α-hydrogen and leading to formation of carbonyl compounds [5].



Nitro esters of N-acetyl and N-dichloroacetyl derivatives of DL- and L-threo- or erythro-1-(p-nitrophenyl)-2-amino-1,3-propanediols were not hydrolyzed on heating or even after prolonged boiling with water.

The process of hydrolysis of nitro esters is known to be accelerated in presence of reducing agents such as urea, HBr, $FeSO_4$, etc. [6]. Experiments were carried out on hydrolysis of nitro esters of N-acyl derivatives of DL- and L-threo-1-(p-nitrophenyl)-2-amino-1,3-propanediols in an aqueous medium in presence of urea; it was established that the chemical behavior of nitro esters of N-acetyl derivatives differed appreciably from that of esters of N-dichloroacetyl derivatives.

Hydrolysis proceeded rapidly when dinitro esters of DL- and L-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediols were boiled in an aqueous medium in presence of urea (2 moles per mole of nitro ester). The yield of "diols" was 90%. The configuration of the alcohol obtained by hydrolysis of the dinitro ester of DL-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol was easily established from its identity with DL-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol, a specimen of which was in our possession.

L-Erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol has not been described. Its N-benzoyl and N-dichloroacetyl derivatives and the unacylated aminodiol have been described [2]. For establishment of the configuration of the product of hydrolysis of the dinitro ester of L-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol, hydrolysis to the corresponding aminodiol was therefore carried out, and its N-benzoyl and N-dichloroacetyl derivatives were prepared; the agreement between specific rotations and melting points demonstrated the identity of the latter three compounds with the corresponding substances described in the literature.

It was thus established that in the hydrolysis of O_1,O_3-dinitro esters of DL- and L-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediols in presence of urea (pH of solution changed from 2 to 5 during the reaction), Walden inversion takes place at the C_1, and hydrolysis accordingly proceeds with rupture of the bond between the carbon and the oxygen ($\geq C \leftarrow ONO_2$), very probably in accordance with a bimolecular mechanism.

Replacement of the N-acetyl group by the more electronegative N-dichloroacetyl group led to a sharp rise in resistance of the nitro esters to hydrolysis. For example, heating of the dinitro esters of DL- and L-threo-1-(p-nitrophenyl)-2-dichloroacetylamino-1,3-propanediols in an aqueous urea solution gave the initial dinitro ester (~68-70%); ionic chlorine was detected in the reaction solution, which indicated partial decomposition of the dichloroacetyl group. The quantity of Cl^- in the reaction solution increased with increasing quantity of urea to 4 moles per mole of dinitro ester and with increasing duration of heating. A proportionately much larger quantity (~67.5%) of the initial dinitro ester was cleaved. In none of the cases was the normal product of hydrolysis isolated, namely DL- or L-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. Walden inversion at the C_1 was observed under the same conditions during hydrolysis of O_1,O_3-dinitro ester of L-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol; in this case, hydrolysis of the nitrate groups was accompanied by hydrolysis of the N-acetyl group, and the reaction gave L-threo-1-(p-nitrophenyl)-2-amino-1,3-propanediol in a yield of 70-75%.

We convey our gratitude to O. Yu. Magidson for the interest which he showed in this investigation.

EXPERIMENTAL

Dinitro ester of DL-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. To a mixture of 50 ml of HNO_3 (d 1.5) and 50 ml of H_2SO_4 (d 1.84) was gradually added 5 g of DL-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol at –2° in the course of 1.5 hr. The reaction mixture was stirred for another 30 min at the same temperature. It was then poured onto ice and the precipitate was filtered off, thoroughly washed with water, pressed, and (without previous drying) crystallized from methanol. Yield 5.57 g (82%) of dinitro ester; a colorless, crystalline substance with m.p. 114-115°.

Found %: N 15.91; C 38.46; H 3.52. $C_{11}H_{12}O_9N_4$. Calculated %: N 16.28; C 38.4; H 3.51.

Dinitro ester of L-(+)-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. Prepared from 5 g of L-(+)-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol by the method described above. The dinitro ester was purified by dissolution in 25 ml of hot methanol, filtration, addition to the cooled filtrate of 3-5 ml of water (until cloudy), standing for 24 hr at 18-20°, cooling, and filtration of the nearly colorless, crystalline substance. M.p. 88-89°, $[\alpha]_D^{20}$ –32° (2% solution in CH_3OH). Yield 5.1 g (75%).

Found %: N 16.21; C 38.10; H 3.47. $C_{11}H_{12}O_9N_4$. Calculated %: N 16.28; C 38.4; H 3.51.

Dinitro ester of DL-threo-1-(p-nitrophenyl)-2-dichloroacetylamino-1,3-propanediol. Prepared by the above-described reaction from 6.46 g of DL-threo-1-(p-nitrophenyl)-2-dichloroacetamino-1,3-propanediol (using the same concentrations of HNO_3 and H_2SO_4). A nearly colorless, crystalline substance, m.p. 117-118° (from methanol); yield 6.83 g (83%).

Found %: N 13.34; Cl 17.25. $C_{11}H_{10}O_9N_4Cl_2$. Calculated %: N 13.56; Cl 17.16.

To a solution of 1.26 g of urea in 15 ml of water was added 4.13 g of dinitro ester, and the mixture was boiled for 2 hr. Some of the initial ester (2.78 g or 67.3%) separated out on cooling. Analysis of the mother liquor revealed a content of 0.21 g of Cl^-, i.e., 29.6% of the chlorine which had been present in the initial dinitro ester. Prolongation of the heating period or an increase in the quantity of urea led to a decrease in the quantity of recovered dinitro ester and to an increase in the Cl^- content of the mother liquor.

Dinitro ester of L-(+)-threo-1-(p-nitrophenyl)-2-dichloroacetylamino-1,3-propanediol. Prepared like the dinitro ester of DL-threo-1-(p-nitrophenyl)-2-dichloroacetylamino-1,3-propanediol. The reaction product (filtered off and washed with water) was dissolved in 30 ml of hot methanol, and the solution was filtered. To the filtrate at

20° was added 5-6 ml of water until the mixture became cloudy; it was then allowed to stand for 24 hr at 18-20°; after cooling, the crystals of dinitro ester were filtered off. M.p. 89-90°, $[\alpha]^{20}_D$ − 22°(2% solution in CH_3OH), yield 6.19 g.

Found %: N 13.67. $C_{11}H_{10}O_9N_4Cl_2$. Calculated %: N 13.56.

Dinitro ester of L-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. To a mixture of 5 ml of HNO_3 (d 1.5) and 5 ml of H_2SO_4 (d 1.84) at −12° was gradually added 3.87 g of L-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. The reaction mixture was stirred at the same temperature for another 30-40 min and then poured onto ice. The resulting precipitate was filtered off, washed with water, and crystallized from methanol. The dinitro ester (4.2 g) was isolated as a colorless, crystalline substance, m.p. 91-92°, $[\alpha]^{20}_D$−6.2° (2% solution in methanol).

Found %: N 16.25. $C_{11}H_{12}O_9N_4$. Calculated %: N 16.28.

Hydrolysis of the dinitro ester of DL-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. A mixture of 6.88 g of dinitro ester and 2.64 g of urea in 15 ml of water was boiled for 2 hr (the initial pH was 2, after 20-25 min it was 4-5, and at the close of boiling it was 5.5-6). The reaction solution was cooled to 40-50°, 3.4 g of $NaHCO_3$ was added, and stirring was continued for 2-3 hr at 18-20°. After the mass was cooled, the precipitate was filtered off and crystallized from methanol. There was obtained 4.5 g (88.5%) of DL-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol; a colorless, crystalline substance with m.p. 190-190.5°. No melting point depression of a mixture with DL-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol prepared by another route.

Found %: N 11.34. $C_{11}H_{14}O_5N_2$. Calculated %: N 11.02.

Hydrolysis of O_1,O_3-dinitro ester of L-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. A mixture of 20.6 g of dinitro ester and 7.55 g of urea in 45 ml of water was boiled for 2 hr (the pH changes were the same as above). At the close of heating the reaction solution was cooled to 40-50°, 10.2 g of $NaHCO_3$ was gradually added, and the mass stirred for 2 hr at 18-20°. L-Erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol came down on cooling and was filtered off.

Yield 13.7 g (90%). M.p. 165-166° (from methanol), $[\alpha]^{20}_D$ +2.5°(2% solution in methanol).

Found %: C 52.04; H 5.56; N 11.23. $C_{11}H_{14}O_5N_2$. Calculated %: C 51.96; H 5.5; N 11.02.

L-Erythro-1-(p-nitrophenyl)-2-amino-1,3-propanediol. A mixture of 7.8 g of L-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol and 16 ml of 20% hydrochloric acid was heated for 2 hr at 70-75°. The hot solution was treated with active carbon, filtered, and cooled to 0 to −2°. The crystals of L-erythro-1-(p-nitrophenyl)-2-amino-1,3-propanediol hydrochloride were filtered off and crystallized from methanol. Yield 5.68 g, m.p. 203-204°, $[\alpha]^{20}_D$ −2.2° (2% solution in ethanol).

An aqueous solution of ammonia was added to a solution of 5.48 g of the hydrochloride in 10 ml of water until the pH was 9-9.5. The mass was then cooled, and the resulting precipitate filtered off and crystallized from methanol. There was obtained 4.42 g of L-erythro-1-(p-nitrophenyl)-2-amino-1,3-propanediol, m.p. 112-113°, $[\alpha]^{20}_D$ −2.5° (2% solution in methanol or ethanol) [2].

L-Erythro-1-(p-nitrophenyl)-2-dichloroacetylamino-1,3-propanediol. To 2 g of L-erythro-1-(p-nitrophenyl)-2-amino-1,3-propanediol in 1.3 ml of anhydrous methanol was added 1.2 ml of methyl dichloroacetate. The mass was boiled for an hour and cooled to 75°, when 4.3 ml of water heated to 70-75° was added, the reaction mixture heated to the boil, cooled to 5°, stirred at this temperature for an hour, and filtered from the resulting crystalline precipitate. Yield 2.64 g, m.p. 179-180° (from methanol), $[\alpha]^{20}_D$ +13.8° (in methanol), $[\alpha]^{20}_D$ +20° (in 4% solution in acetone) [2].

L-Erythro-1-(p-nitrophenyl)-2-benzoylamino-1,3-propanediol. To a suspension of 6 g of L-erythro-1-(p-nitrophenyl)-2-amino-1,3-propanediol in 30 ml of anhydrous benzene was gradually added 4.8 g of benzoyl chloride with stirring at 5-10°. Stirring was continued for another 30 min at the same temperature and for 2 hr at 40-45°. The reaction mixture was cooled, and the precipitate filtered and crystallized from methanol. Yield 7.96 g, m.p. 216-217°, $[\alpha]^{20}_D$ +114.6° (2% solution in dimethylformamide) [2].

Hydrolysis of dinitro ester of L-erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol. A mixture of 2 g of dinitro ester and a solution of 0.77 g of urea in 4.5 ml of water was boiled for 2 hr. It was then cooled and NH_4OH

was added at 40° until the color to phenolphthalein was pink; the reaction solution was then treated with ethyl acetate for extraction of L-threo-1-(p-nitrophenyl)-2-amino-1,3-propanediol. Yield 0.69 g, m.p. 161-162° (from methanol), $[\alpha]^{20}_D$ +18.5° (2% solution in ethanol) [7].

Reaction of dinitro ester of L-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol with NaOH solution. Into a suspension of 1.72 g of dinitro ester in 5 ml of 95% alcohol at 10-15° was stirred 0.93 ml of 40% aqueous NaOH solution. Stirring was continued for 3 hr at 10-15°, the mass was cooled to 0 to −2°, and the precipitate was filtered off, dried, and dissolved in 10% acetic acid solution (to give a total volume of 10 ml). To 1 ml of this solution was added 1 ml of 10% NaI solution. The mixture was left in the dark for 30 min and then titrated with 0.1 N $Na_2S_2O_3$. The titration value indicated a content of 0.672 g $NaNO_2$ in the isolated precipitate. The alcoholic mother liquor was poured into 100 ml of water and acidified with 10-15% hydrochloric acid. The resulting amorphous precipitate had m.p. 172-178°, was easily soluble in nearly all organic solvents, and was difficult to purify.

Similar results were obtained on interaction of the dinitro ester of L-threo-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediol with a solution of alkali in dilute alcohol.

SUMMARY

1. Hydrolysis of O_1,O_3-dinitro esters of DL- and L-threo- or erythro-1-(p-nitrophenyl)-2-acetylamino-1,3-propanediols is effected with facility, with a high yield of hydrolysis product, by heating in an aqueous medium in presence of urea (pH 2-5). This process is shown to be accompanied by Walden inversion at the C_1 with interconversion of the diastereoisomeric threo- and erythro-forms.

2. Replacement in the above-mentioned dinitro esters of the N-acetyl residue by the N-dichloroacetyl residue considerably increases the resistance of the nitro groups to hydrolysis. If the dinitro esters of 1-(p-nitrophenyl)-2-dichloroacetylamino-1,3-propanediones are boiled in an aqueous medium in presence of urea, the nitro groups are not hydrolyzed but the dichloroacetyl group breaks down (with separation of Cl^-) to an extent directly proportional to the period of heating and the quantity of urea.

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MONOSACCHARIDES

I. A NEW SYNTHESIS OF D-QUINOVOSE AND D-FUCOSE

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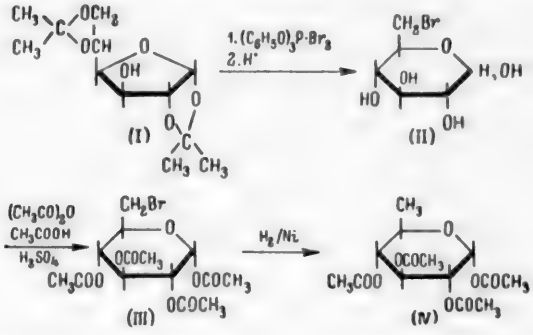
One of the most important unsolved problems of monosaccharide chemistry is the development of methods of direct replacement of a hydroxyl group in a molecule of suitably protected monosaccharide by other substituents. A few reactions of this type are known only for primary hydroxyls, and it is virtually true that such a technique is unknown in the case of secondary hydroxyl groups, although the value of such reactions in the synthesis of deoxysugars, aminosugars, etc. is obvious.

Recently we published the results [1] of a study of the reaction of 1,2-5,6 -diisopropylidene-D-glucofuranose (diacetoneglucose) (I), selected as a first model substance, with complexes of triphenyl phosphite with halogens (bromine, iodine). This reaction actually leads to replacement of a hydroxyl group by halogen if it is performed under mild conditions; contrary to expectation, however, the product was not 3-halo-3-deoxyhexose but the 6-halo-6-deoxy derivative (II). A more detailed study of the reaction showed that, in spite of the relatively low yield of halosugar, its simplicity rendered it of definite interest for the synthesis of 6-deoxy-D-glucose (D-quinovose). Our original method [1] of direct hydrogenation of 6-halo-6-deoxy-D-glucose to D-quinovose gave a mixture of products of reduction since the carbonyl group evidently did not remain inert under these conditions. In the present work we therefore converted 6-bromo-6-deoxy-D-glucose into crystalline α-tetraacetyl-6-bromo-6-deoxy-D-glucopyranose (III), hydrogenation of which over skeletal nickel led to 1,2,3,4-tetraacetyl-D-quinovose (IV).



The experimental results show that the complex of triphenyl phosphite with bromine reacts with diacetoneglucose with formation of 6-bromo-6-deoxy-D-glucose, and not of the expected 3-bromo-3-deoxy derivative. A similar results was obtained earlier [2] in a study of the reaction of diacetoneglucose with phosphorus pentachloride, which also led to replacement of the primary hydroxyl at C_6 by halogen. The cause of this phenomenon is obscure, and two different explanations may be advanced [1]; however, it is natural to suggest that replacement of the secondary hydroxyl at the C_3 does not take place simply because of the possibility of substitution at the more reactive and insufficiently screened primary hydroxyl. In order to test this hypothesis we attempted to replace a secondary hydroxyl by halogen in an analog of diacetoneglucose with a more effectively screened primary hydroxyl. The analog in question was 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose, which was prepared by the known route [3, 4], but with systematic modifications. In the case of this compound the detachment of the methyl group at the C_6 is definitely excluded under mild reaction conditions. It was found that 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose

does not react with triphenyl phosphite dibromide and triphenyl phosphite diiodide under our chosen conditions, i.e., in anhydrous benzene at room temperature; the reaction does not go even with heating. The monosaccharide was also recovered unchanged after many hours' boiling of 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose with phosphorus pentachloride in absolute xylene. These results show that also in this case replacement of the secondary hydroxyl at the C_3 by halogen does not take place under the action of triphenyl phosphite complexes and even of phosphorus pentachloride when the primary hydroxyl of a saccharide is sufficiently well protected. In all probability this is associated with the difficulty of attack of the C_3 atom from the adequately screened rear side which would be required for replacement of a hydroxyl by the S_N2 mechanism.

Consequently the employment of complexes of triphenyl phosphite with halogens for replacement of secondary hydroxyl groups of saccharides which at any rate are sterically hindered, as in the case of diacetoneglucose, does not lead to the desired result. At the same time primary hydroxyl groups are evidently quite easily replaced by halogen under the action of the above reagents, and this is of some preparative interest since hitherto the synthesis of 6-halo-6-deoxyhexoses from 5-halo-5-deoxypentoses in acceptable yields was only possible in two steps via 6-tosyl esters. In illustration of the synthetic value of our proposed reaction, we also effected a new synthesis of D-fucose by a scheme similar to that for quinovose.

Reaction of 1,2-3,4-diisopropylidene-D-galactopyranose with the complex of triphenyl phosphite with bromine in anhydrous benzene at room temperature, followed by hydrolysis, gave syrupy 6-bromo-6-deoxygalactose which was converted into tetraacetyl-6-bromo-6-deoxy-D-galactose (also in syrupy form). Hydrogenation of the latter over skeletal nickel led to tetraacetyl-D-fucose which was then deacetylated by sodium methoxide. The resulting D-fucose was identified in the form of the benzylphenylhydrazone.

The data presented in this paper show that complexes of triphenyl phosphite with halogens may be of interest for direct replacement of primary hydroxyl groups in carbohydrates by halogen.

EXPERIMENTAL

The R_f values given were obtained on ascending chromatograms with the help of the solvent system n-butanol : : water : acetic acid 4 : 2 : 1 also used for partition chromatography on cellulose (system A), and of the system n-butanol : water 86 : 14 (system B). Chromatographic paper M of the No. 2 Leningrad Factory was used; the stains were developed with p-anisidine– H_3PO_4; hydrolysis was performed by heating for 30 min with 1% H_2SO_4 and 50% aqueous methanol at 100° prior to chromatography of the isopropylidene derivatives.

6-Bromo-6-deoxy-D-glucose was prepared from 0.03 mole of 1,2-5,6-diisopropylidene-D-glucofuranose as described earlier [1]. Yield 16.5%; $[\alpha]_D^{19}$ +43° (c 4.45, water). Literature data [5]: $[\alpha]_D^{17}$ +49° (c 4.04, water).

α-Tetraacetyl-6-bromo-6-deoxy-D-glucopyranose. A solution of 300 mg of 6-bromo-6-deoxy-D-glucose in a mixture of 14 ml of acetic anhydride and 7 ml of glacial acetic acid was cooled to 0°; 14 drops of conc. H_2SO_4 were then added and the mixture allowed to stand at 0° for 24 hr. The reaction mixture was poured into ice water, and the precipitated amorphous α-tetraacetyl-6-bromo-6-deoxy-D-glucopyranose extracted with chloroform. The extract was washed with sodium carbonate solution and with water, dried, and evaporated in vacuo. The residue was crystallized from methanol to give fine needles. Yield 200 mg.

M.p. 170-170.5° $[\alpha]_D^{24}$ +110° (c 7.66, $CHCl_3$). Literature data [6]: m.p. 172-173°, $[\alpha]_D^{24}$ + 110.6° (c 7.85, $CHCl_3$).

α-Tetraacetyl-D-quinovose. A solution of 252 mg of α-tetraacetyl-6-bromo-6-deoxy-D-glucopyranose in 15 ml of methanol, to which 5 drops of diethylamine was afterwards added, was hydrogenated over skeletal nickel at room temperature until hydrogen absorption ceased. After filtration, the solution was diluted with an equal volume of water and extracted with ether. The extract was dried and evaporated in vacuo. The residue was crystallized from n-butanol, and α-tetraacetyl-D-quinovose was obtained in a yield of 100 mg, m.p. 114.5-115°. Literature data [7]: m.p. 117°.

6-Bromo-6-deoxy-D-galactose. To 9.3 g of triphenyl phosphite was added a solution of 2.4 g of bromine in 25 ml of absolute benzene, and then a benzene solution of 7.8 g of 1,2-3,4-diisopropylidene-D-galactopyranose. After the lapse of 72 hr the benzene was taken off in vacuo. To the residue was added 200 ml of 50% methanol, and 1 ml of conc. H_2SO_4, and the mixture boiled for 3 hr. After cooling, the aqueous methanolic solution was exactly neutralized with $Ba(OH)_2$ solution, and the solution was centrifuged, boiled for a short period with active carbon, and evaporated in vacuo. The residue was a syrupy mixture of saccharides whose chief component had R_f

0.49 (system A). Chromatography on cellulose gave chromatographically pure, syrupy 6-bromo-6-deoxy-D-galactose. Yield 1.5 g (20.5%), $[\alpha]^{23}_D$ +56° (c 6.56, water).

Tetraacetyl-6-bromo-6-deoxy-D-galactose. The bromo compound (0.5 g) was acetylated by the above procedure for tetraacetyl-6-bromo-6-deoxy-D-glucose to give syrupy tetraacetyl-6-bromo-6-deoxy-D-galactose. Yield 0.4 g, $[\alpha]^{24}_D$ +63° (c 5.43, $CHCl_3$).

Found %: C 40.72, 40.66; H 4.69, 4.73; Br 19.73, 19.76. $C_{14}H_{19}O_9Br$. Calculated %: C 40.89; H 4.66; Br 19.43.

Benzylphenylhydrazone of 6-deoxy-D-galactose (D-fucose). To a solution in 20 ml of methanol of 350 mg of tetraacetyl-6-bromo-6-deoxy-D-galactose (prepared in the preceding experiment) was added 5 drops of diethylamine. Hydrogenation was effected at room temperature over skeletal nickel until hydrogen absorption ceased. The catalyst was filtered off, and the filtrate diluted with an equal volume of water and extracted with ether. The extract was dried and evaporated in vacuo; the residue (a colorless, thick syrup) was dissolved in 2 ml of chloroform and treated with a solution of 0.3 g of sodium in 1.5 ml of methanol at 0°. After an interval of 15 min, 1.5 ml of water and a few drops of acetic acid were added to the reaction mixture. The aqueous layer was separated and evaporated in vacuo. To the residue, dissolved in alcohol, was added 15 drops of benzylphenylhydrazine; the mixture was heated for 5 min and allowed to stand overnight at room temperature. A precipitate was formed on addition of water, and was separated, washed with ether, and recrystallized three times from methanol. Yield of D-fucose benzylphenylhydrazone 60 mg, m.p. 174-175°.

$[\alpha]^{22}_D$ −16° (c 0.79, CH_3OH). Literature data [8]: m.p. 178-179°, $[\alpha]_D$ −14.9° (CH_3OH).

Found %: C 66.25, 66.57; H 6.94, 6.83. $C_{19}H_{24}O_4N_2$. Calculated %: C 66.26; H 7.02.

1,2-5,6-Diisopropylidene-3-O-benzyl-D-glucofuranose. Purification of 34.5 g of 1,2-5,6-diisopropylidene-3-O-benzyl-D-glucofuranose (prepared by the known method [3]) was effected by chromatography in a column containing 300 g of Al_2O_3, with hexane as eluting medium. Yield of pure product 30 g; hydrolysis followed by paper chromatography led to development of a single stain with R_f 0.65 (system B), corresponding to 3-O-benzyl-D-glucose

1,2-Isopropylidene-3-O-benzyl-D-glucofuranose. A mixture of 18.75 g of 1,2-5,6-diisopropylidene-3-O-glucofuranose, 56 ml of glacial acetic acid, and 33 ml of water was held for 5 hr at 34°, and then evaporated in vacuo. The residue was dissolved in 100 ml of ether, and the solution washed with sodium carbonate solution and water, dried over anhydrous magnesium sulfate, and evaporated for removal of the ether. Yield of syrupy 1,2-isopropylidene-3-O-benzyl-D-glucofuranose 15.45 g (92%). The product was identified by conversion of a portion with acetic anhydride in pyridine to give the 5,6-diacetyl derivative, m.p. 119° (from CH_3OH). The literature [3] gives m.p. 119-120°.

1,2-Isopropylidene-3-O-benzyl-5,6-di-O-methyl-D-glucofuranose. To a solution of 12 g of 1,2-isopropylidene-3-O-benzyl-D-glucofuranose in 100 ml of benzene was added 8 g of NaOH powder and 25 g of dimethyl sulfate. The reaction mixture was stirred for an hour at 20° and for 3 hr at 50°, after which the benzene solution was separated. The operation was repeated. Addition of 25 ml was subsequently made, and the mixture was refluxed for an hour. The benzene layer was separated, washed with water, dried over anhydrous magnesium sulfate, and evaporated; the residue (13 g) was chromatographed in a column containing 200 g of Al_2O_3 and eluted with benzene. Yield of syrupy 1,2-isopropylidene-3-O-benzyl-5,6-di-O-glucofuranose 10 g (76%); b.p. 130-135° (0.1 mm). The literature [4] gives b.p. 160° (0.2 mm). After hydrolysis, the product was chromatogrammed on paper and gave a single stain with R_f 0.85 (system B) corresponding to 3-O-benzyl-5,6-di-O-methyl-D-glucofuranose.

1,2-Isopropylidene-5,6-di-O-methyl-D-glucofuranose. A solution of 10 g of 1,2-isopropylidene-3-O-benzyl-5,6-di-O-methyl-D-glucofuranose in 75 ml of alcohol was boiled for 5 hr with 15 g of skeletal nickel, after which another 5 g of skeletal nickel was added, and boiling continued for 3 hr. The mass was filtered, the solid washed with alcohol, and the solution evaporated to leave a residue which was then distilled in vacuo. Yield of 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose 6 g (82%).

B.p. 108-109° (0.2 mm), m.p. 52-53° (from hexane). Literature data: b.p. 122° (0.4 mm) [4], 105-110° (0.15 mm), m.p. 56° (from ligroine) [9].

After hydrolysis, the product was chromatogrammed on paper to give a single stain with R_f 0.52 (system B), corresponding to 5,6-di-O-methyl-D-glucofuranose. Boiling of 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose with phenyl isocyanate in benzene gave the phenylurethane of 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose, m.p. 86-87°. Literature data [9]: m.p. 88-89° (from aqueous alcohol).

Reaction of 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose with halogen – triphenyl phosphite complexes and phosphorus pentachloride. To 310 mg of triphenyl phosphite was added a solution of 250 mg of iodine in 5 ml of anhydrous benzene, and then a solution of 250 mg of 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose in 5 ml of benzene. The mixture was left for two days at 20°. Part of the reaction mixture (1 ml) was hydrolyzed by boiling with 1% H_2SO_4 solution in 50% aqueous methanol, and after neutralization it was chromatogrammed on paper to give solely a stain of 5,6-di-O-methyl-D-glucofuranose with R_f 0.52 (system B). The reaction mixture was heated for another 6 hr on a water bath; during this operation considerable resinification was observed; chromatography on paper of the products of hydrolysis again gave only the stain of the 5,6-di-O-methyl-D-glucofuranose formed on hydrolysis of the initial compound.

Reaction of 310 mg of triphenyl phosphite, 260 mg of bromine, and 250 mg of 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose in 10 ml of benzene under similar conditions likewise gave a product which after chromatography on paper gave a stain corresponding to the original substance.

A solution of 470 mg of phosphorus pentachloride and 100 mg of 1,2-isopropylidene-5,6-di-O-methyl-D-glucofuranose in 25 ml of absolute xylene was boiled for 45 hr. In the course of this operation the reaction mixture only yellowed slightly. Only 5,6-di-O-methyl-D-glucofuranose (R_f 0.52, system B) was detected by paper chromatography of the products of hydrolysis of the reaction mixture as described above.

SUMMARY

1. It is shown that reaction of 1,2-5,6-diisopropylidene-D-glucofuranose and 1,2-3,4-diisopropylidene-D-galactopyranose with triethyl phosphite – bromine complex gives respectively 6-bromo-6-deoxy-D-glucose and 6-bromo-6-deoxy-D-galactose, which by acetylation, followed by hydrogenation of the acetyl compounds, are converted into derivatives of D-quinovose and D-fucose.

2. It was established that the secondary hydroxyl at the C_3 in 1,2-diisopropylidene-5,6-di-O-methyl-D-glucofuranose is not replaced by a halogen atom either by the action of complexes of triphenyl phosphite with bromine and iodine or by the action of phosphorus pentachloride.

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INVESTIGATION OF THE REACTION OF BENZENE WITH PHENYL DERIVATIVES OF ELEMENTS OF THE FOURTH GROUP OF THE PERIODIC SYSTEM AND THE DETERMINATION OF THE COMPOSITION OF THEIR MOLECULAR COMPOUNDS BY THE METHOD OF LABELED ATOMS

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At the beginning of 1958 a paper appeared by L. A. Korshunov and A. A. Orlova [1] which reported that tetraphenyllead does not exchange phenyl groups with benzene. According to our data this cannot be confirmed; tetraphenyllead exchanges with benzene although to a very slight extent – up to 0.75% after 20 hr at 200° (Table 1). During the work it was also found that tetraphenyllead, tetraphenyltin, and tetraphenylsilicon give molecular compounds with benzene with the general formula $[E(C_6H_5)_4]_7 \cdot C_6H_6$, where E = Si, Sn, Pb.

Detection of the molecular compounds of tetraphenyl-metals with benzene, and in turn the establishment of their composition, is only possible with the help of labeled benzene (Table 2) due to the percentage content of carbon in all these compounds being close to its content in the free tetraphenyl-metal.

We failed to find in the literature any reference to the existence of the molecular compounds tetraphenylsilicon, tetraphenyltin, or tetraphenyllead that we had detected, but Anschütz [1] reported that triphenylmethane gives a molecular compound with benzene in 1 : 1 ratio. In his investigation this author carried out the analysis on triphenylmethane which had been recrystallized from benzene and freed of excess benzene by pressing on filter paper. We prepared this molecular compound by Anschütz's procedure and found that it differed from the molecular compounds of benzene with tetraphenylsilicon, -tin, and -lead in being very unstable. After overnight standing its activity fell by a factor of 10, and after drying in vacuo at 70° for 4 hr it retained only a small part of its activity. Due to this degree of instability, the analysis of this molecular compound cannot give accurate results (Table 3).

The results of analyses depend on the period spent in preparation of the sample for analysis: during the very short period (10-15 min) spent in weighing, the ratio changes from 1 : 2 to nearly 2 : 1, and the mean value is 1 : 1, as found by Anschütz [1].

EXPERIMENTAL

The benzene used in exchange experiments as well as for preparation of C^{14}-labeled molecular compounds was dried with metallic sodium and distilled.

Compounds $E(C_6H_5)_4$ (where E = Si, Sn, Pb) were recrystallized from ligroine which had been thoroughly freed of unsaturated compounds.

Combustion of molecular compounds and of benzene for analysis of their activity was performed by wet oxidation with Van Slyke-Folch mixture. The carbon dioxide was absorbed in saturated barium hydroxide solution, which was thereupon filtered through a small perforated dish, washed, and dried. Reading of the activity of the sample (using a MSG-17 end-face counter) was performed in the course of 5 min, and these readings alternated with readings of the background activity. Not fewer than five readings were taken for each sample.

Exchange experiments with benzene were carried out in glass ampoules. After drying at 120-150°, the hot ampoules were cooled under nitrogen. Their filling and subsequent sealing were likewise effected under nitrogen. Results of exchange experiments are set forth in Table 1.

TABLE 1

First component	Molar ratio	Temperature	Activity of benzene (in μ Cu / mole)	Activity of first component after experiment		Exchange judging by appearance of activity in first component in course of 20 hr
				in $\frac{\mu Cu}{mole}$	in % of initial activity	
Triphenylmethane	1 : 3	100	81.8	None	–	None
	1 : 6	200	81.8	Traces	–	Traces
Tetraphenylsilicon	1 : 8	200	81.8	Traces	–	Traces
Tetraphenyltin	1 : 16	200	81.8	Traces	–	Traces
Tetraphenyllead	1 : 16	150	90.4	1.95	0.13	0.67
	1 : 16	200	90.4	2.16	0.15	0.75

TABLE 2

Activity of $BaCO_3$ in pulses per min obtained from		Activity of $BaCO_3$ in pulses/min calc. for $[E(C_6H_5)_4)_x \cdot C_6H_6$ where			Formula established for molecular compound on the basis of the activity
$[E(C_6H_5)_4]_x C_6H_6$	initial benzene	$x = 6$	$x = 7$	$x = 8$	
E = Si 163 ± 3	4738 ± 15	190.0	163.4	143.6	$[E(C_6H_5)_4]_7 \cdot C_6H_6$
Sn 165 ± 3	4834 ± 39	193.3	166.7	146.5	
Pb 156 ± 3	4765 ± 97	190.6	164.3	144.4	

TABLE 3

Conditions for preparation of substance for analysis		Activity of $BaCO_3$ in pulses/min obtained		Calculated activity of $BaCO_3$ in pulses/min for $(C_6H_5)_3CH \cdot C_6H_6$ in ratios of		
drying	weight of sample	from molecular compound	from original benzene	1 : 1	1 : 2	2 : 1
Pressed with filter paper until dry	0.1044	1001 ± 4	5883 ± 6	1412	–	802
Pressed with a filter paper, then spread over another and again pressed	Without weighing	658 ± 10	3466 ± 98	832	–	472
Pressed with filter paper until dry without spreading over another filter paper	Without weighing	2359 ± 14	5704 ± 23	1369	2208	–

Molecular compounds of tetraphenyl-metals. The compound $E(C_6H_5)_4$ was placed in a dry ampoule and benzene was added (1 : 15 molar ratio). The ampoule was then sealed under nitrogen and heated at 150° in a thermostat until the $E(C_6H_5)_4$ dissolved in the benzene (30-35 min). The cooled ampoule was opened and the excess of benzene distilled in a nitrogen stream into a trap cooled with a mixture of dry ice and acetone. The dry residue was transferred to a glass which was left uncovered in a fume hood. The latter was then placed for storage in a desiccator containing calcium chloride and paraffin wax.

In a special experiment it was found that when kept in an open dish in the air, the molecular compound of tetraphenylsilicon and benzene did not change in activity in the course of a month (the test was not continued for a longer period). In the case of the tetraphenyllead- and -tin compounds with benzene, the activity fell very slightly on keeping in the air. The activity of samples did not alter drying in vacuo (residual pressure 50 mm) at 100° for 5 hr.

Molecular compounds of tetraphenylsilicon-, tin, and -lead do not possess melting points (they decompose in the vicinity of the melting points of the original tetraphenyl-metals).

Results of analyses of molecular compounds of tetraphenyl-metals with benzene are set forth in Table 2.

The molecular compound of triphenylmethane and benzene was prepared by the method of Anschütz [2] and found to be very unstable. Results of three analyses are set forth in Table 3.

SUMMARY

1. Tetraphenylsilicon, tetraphenyltin, and tetraphenyllead are found to form with benzene stable compounds with the general formula $[E(C_6H_5)_4]_7 \cdot C_6H_6$. The molecular compound of triphenylmethane with benzene (1 : 2) is very unstable.

2. A method is advanced for determination of the composition of molecular compounds of elementoorganic compounds with C^{14}-labeled solvents (the method is only applicable in the absence of exchange of groups with the solvent).

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THE ACTION OF TRIISOBUTYLALUMINUM ON CYCLOHEXANONE

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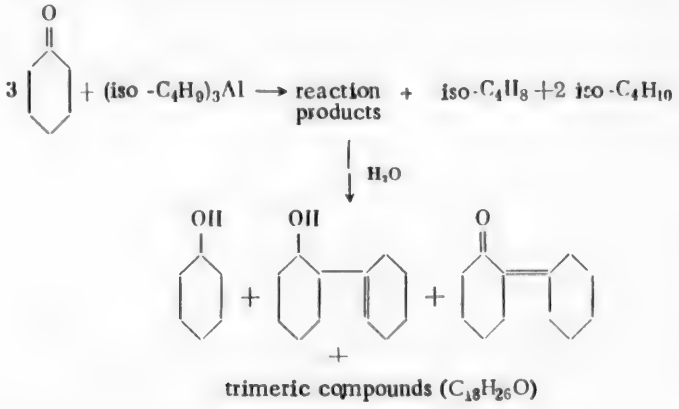
The action of triisobutylaluminum on cyclohexanone was first studied by Ziegler and co-workers [1]. Reaction of 1 mole of cyclohexanone with 1 mole of triisobutylaluminum is accompanied by reduction of the cyclohexanone and by release of a mole of isobutylene. Two additional moles of cyclohexanone then react in such a manner that an aluminum enolate is formed and isobutane is the main product released. Hydrolysis of the reaction mass gives a mixture of cyclohexanol and cyclohexanone.

Investigation of this reaction led to results differing from those of Ziegler and co-workers, although outwardly the reaction proceeds as described. Addition of 1 mole of cyclohexanone to 1 mole of triisobutylaluminum at 50-60° in toluene solution or in the absence of solvent leads to release of about 1 mole of gas containing 86-88% of isobutylene and 12-14% of isobutane. Subsequent addition of 2 moles of cyclohexanone results in evolution of about 2 moles of gas containing 9% of isobutylene and 91% of isobutane. The following were isolated after hydrolysis of the reaction products: cyclohexanol in the amount of about 0.5 mole in admixture with a little cyclohexanone, a mixture of approximately equal amount (more than 1.5 moles calculated as cyclohexanone) of 1-cyclohexylidene-2-cyclohexanone and 1-cyclohexenyl-2-cyclohexanol, and a mixture of trimeric compounds with the formula $C_{18}H_{26}O$ (about 1 mole calculated as cyclohexanone) whose structure was not established. The ratio of dimeric to trimeric products varies with the experimental conditions. The absence of appreciable amounts of cyclohexanone is an indication of the nonformation of an aluminum enolate in this reaction. Cyclohexanol was isolated in good yield after hydrolysis of the products of reaction of 1 mole of cyclohexanone with 1 mole of triisobutylaluminum, in agreement with the findings of Ziegler and co-workers.

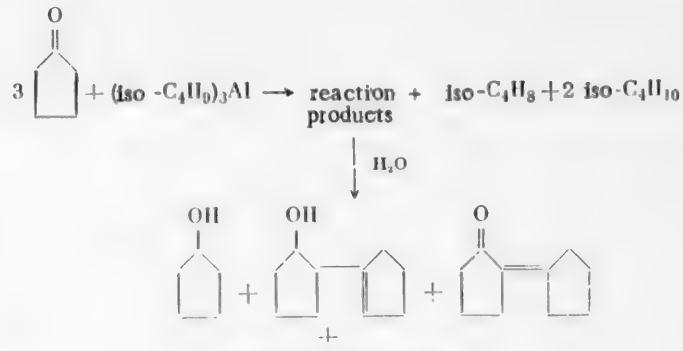
It follows from the above results that reaction of cyclohexanone with triisobutylaluminum takes the following course. Reaction of equimolar amounts of cyclohexanone and triisobutylaluminum leads to release of isobutylene and to reduction of cyclohexanone with formation of the aluminum alcoholate $(iso\text{-}C_4H_9)_2AlOC_6H_{11}$. This alcoholate promotes condensation of cyclohexanone with formation of dimeric and trimeric ketones and separation of water. Reaction of the water with the organoaluminum compound gives isobutane. Since reduction is the main process in the first reaction step and the evolved gas contains only a small proportion of isobutane, it may be suggested that the rate of reduction of cyclohexanone by triisobutylaluminum is greater than the rate of condensation of cyclohexanone under the action of the alcoholate. Part of the dimeric and trimeric ketones fromed in the process of condensation of cyclohexanone undergoes Meerwein – Ponndorf reduction in the course of the reaction, with participation of the



aluminum alcoholate, to give alcoholates of dimeric and trimeric products and cyclohexanone, the latter again undergoing condensation. This process would account for the decreased quantity of cyclohexanol obtained in the action of 3 moles of cyclohexanone in comparison with the amount resulting from the action of 1 mole of cyclohexanone on triisobutylaluminum. This was confirmed in the case of interaction of diisobutylisopropoxyaluminum $(iso\text{-}C_4H_9)_2AlOC_3H_7$-iso with 2 moles of cyclohexanone. During the reaction 2 moles of gas containing 3.5% of isobutylene and 96.5% of isobutane are evolved, and acetone is formed. Hydrolysis of the reaction products yielded cyclohexanol and a mixture of dimeric and trimeric compounds. The reaction with diisobutylethoxyaluminum goes similarly. Reaction of cyclohexanone with triisobutylaluminum can according be expressed by the above scheme.

The reaction of 4-methylcyclohexanone and of cyclopentanone with triisobutylaluminum resembles the reaction of cyclohexanone. The reaction of 4-methylcyclohexanone gives 4-methylcyclohexanol, dimeric and trimeric products, butane, and isobutylene. The structure of the dimeric products – a mixture of 1-methyl-3-(4-methylcyclohexenyl)-4-cyclohexanone and 1-methyl-3-(4-methylcyclohexenyl)-4-cyclohexanol – was established by their conversion into 1-methyl-3-(4-methylcyclohexyl)-4-cyclohexanone.

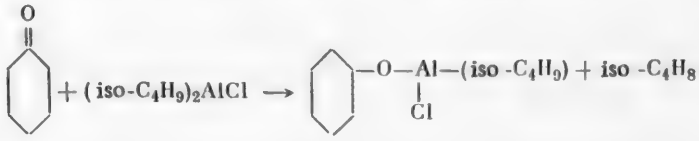
In the case of cyclopentanone the products were cyclopentanol, a mixture of dimeric and trimeric products, butane, and isobutylene. The dimeric products were a mixture of 1-cyclopentylidene-2-cyclopentanone and 1-cyclopentenyl-2-cyclopentanol.



trimeric compounds

It was indicated above that diisobutylalkoxyaluminum $(iso\text{-}C_4H_9)_2AlOR$ · (R = C_2H_5, iso-C_3H_7) in great measure promotes the condensation of cyclohexanone. Reaction of 1 mole of cyclohexanone with 1 mole of diisobutylethoxyaluminum, for example, leads to evolution of a gas consisting of 81% isobutane and 19% isobutylene, while on reaction of a second mole of cyclohexanone the gas consists of 91.5% isobutane and 8.5% isobutylene.

It was found that, unlike alkoxy derivatives, diisobutyl aluminum chloride mainly behaves like a reducing agent in the manner of triisobutylaluminum. Reaction of 1 mole of cyclohexanone with 1 mole of diisobutylaluminum chloride gave a gas consisting of a mixture of 92.5% isobutylene and 7.5% isobutane. Hydrolysis gave cyclohexanol in high yield. This reaction may be represented by the following scheme.



Even the reaction with a second mole of cyclohexanone is accompanied in substantial measure by reduction: the resulting gas consists of 63% isobutylene and 37% isobutane. The reducing properties of diisobutylaluminum chloride will be the subject of another paper.

EXPERIMENTAL

Interaction of triisobutylaluminum with 3 moles of cyclohexanone. a) To a solution of 38.7 g (0.19 mole) of triisobutylaluminum in 60 ml of dry toluene was added 17.6 g (0.18 mole) of cyclohexanone with stirring at 48-52°; the mixture was thereupon heated to 70-80° for 1.5 hr. A gas (10.1 g) was collected in a trap; it consisted of 86% isobutylene and 14% isobutane.

To the reaction mixture was added a further 35.2 g of cyclohexanone with heating to 60-65°. The mixture was heated for an hour to 80°. In a trap was collected 18.2 g of gas, and in subsequent heating for half an hour to 90° 19.5 g of gas was collected with a composition of 9% isobutylene and 91% isobutane.

The reaction mixture was decomposed by dilute sulfuric acid at 0-10°. The toluene layer was separated. The aqueous layer was extracted several times with toluene, and the extracts washed with sodium bicarbonate solution and water, and dried over sodium sulfate. The toluene was driven off and the residue distilled to give the following fractions: 1st, 73-75° (23 mm), 8.2 g; 2nd, 88-90° (2 mm), 24.8 g; 3rd, residue in flask, 10.3 g.

1st fraction: b.p. 64-65° (from 13 mm), 8.2 g; a mixture of 3% cyclohexanone and 97% cyclohexanol.

2nd fraction: b.p. 74-75° (1 mm), $n^{21.5}_D$ 1.5088, 24.8 g; a mixture of 49.5% of 1-cyclohexylidene-2-cyclohexanone [2,4-dinitrophenylhydrazone m.p. 128-130° (from alcohol); literature [2]: m.p. 129-130°] and 50.5% 1-cyclohexenyl-2-cyclohexanol [phenylurethane m.p. 118.5-119.5° (from methanol); literature [3]: m.p. 118-119°.

Hydrogenation of 15 g of this mixture was effected in presence of 2 g of $Pd/BaSO_4$ in 55 ml of alcohol and 0.8 ml of acetic acid. There was obtained 13.6 g of a mixture of 1-cyclohexyl-2-cyclohexanone and 1-cyclohexyl-2-cyclohexanol with b.p. 102-104° (2 mm), n^{18}_D 1.4957.

To 12.6 g of newly prepared mixture in 25 ml of acetic acid was added 3.2 g of chromic acid in 25 ml of acetic acid and 3 ml of water at such a rate that slight heat was developed. The reaction mixture was then heated to 50° for 15 min. After cooling, water was added, the oil was extracted with ether, and the extract was washed with water and dried over sodium sulfate. The ether was taken off and the residue distilled to give 8.4 g of 1-cyclohexyl-2-cyclohexanone:

B.p. 98-100° (2 mm), n^{20}_D 1.4901, d_4^{20} 0.9784.

Semicarbazone: m.p. 176-177° (from methanol); oxime: m.p. 98-99° (from methanol).

Literature data [5, 6]: 1-cyclohexyl-2-cyclohexanone, n^{20}_D 1.4915, $d_4^{19.6}$ 0.9736; semicarbazone (low-melting form): m.p. 174-176°; oxime: m.p. 100°.

3rd fraction: b.p. 180-200° (2 mm), n^{21}_D 1.5285, 10.3 g; evidently a mixture of 2,6-dicyclohexylidene-1-cyclohexanone and 2-cyclohexenyl-6-cyclohexylidenecyclohexanone [4].

Found %: C 83.56, 83.63; H 9.91, 10.13. $C_{18}H_{26}O$. Calculated %: C 83.66; H 10.14.

b) To 24.5 g (0.12 mole) of triisobutylaluminum was added 10.78 g (0.11 mole) of cyclohexanone at 52-60° with vigorous stirring. Towards the end of the addition the temperature had risen to 70°. In the trap was collected 6.1 g of gas containing 80% of isobutylene and 20% of isobutane.

To the solidified reaction product was added 21.56 g (0.22 mole) of cyclohexanone with stirring and heating to 70-80°. In the course of the addition it was necessary to raise the temperature to 90-94° since the reaction went very irregularly with violent frothing of the mass. After one half of the total quantity of cyclohexanone had been added, the temperature rose spontaneously to 150°, and the remainder of the ketone was added at 80-90°. In the trap was collected 12.7 g of gas containing 11% of isobutylene and 89% of isobutane.

To the reaction mass was added 100 ml of dry ether, and dilute sulfuric acid was added 0-8°. After attainment of room temperature, the ethereal layer was collected and the aqueous layer extracted several times with ether. The ethereal extracts were washed with sodium bicarbonate solution and water, and dried over sodium sulfate. The ether was taken off and the residue of 28.4 g distilled to give 3.8 g of cyclohexanol, 12.1 g of a mixture of dimeric products, and 10.6 g of a mixture of trimeric products.

Reaction of triisobutylaluminum with 1 mole of cyclohexanone. To 24.3 g (0.12 mole) of triisobutylaluminum was added 10.7 g (0.11 mole) of cyclohexanone at 52-58°; the temperature rose to 70° at the close of the operation. In the trap was collected 6.2 g of gas containing 88% of isobutylene and 12% of isobutane.

To the reaction mixture was added 30 ml of absolute ether and decomposition was performed on the same lines as in preceding experiments. After the ether had been taken off, 8.5 g of cyclohexanol was isolated.

Reaction of diisobutylethoxyaluminum with cyclohexanone. Into 42 g (0.22 mole) of diisobutylethoxyaluminum in 40 ml of anhydrous toluene was stirred dropwise 20 g (0.20 mole) of cyclohexanone; the temperature rose spontaneously to 50-60°. Heating for 0.5 hr at 80° led to collection of 12.6 g of gas containing 19% of isobutylene and 81% of isobutane.

To the reaction mass was added an additional 20 g of cyclohexanone with heating to 60-70°. After 1.5 hr's heating at 80-90°, 10.6 g of gas was collected with a content of 8.5% isobutylene and 91.5% isobutane. Decomposition of the reaction mixture in the usual manner and distillation of the toluene gave a residue from which by distillation was obtained 8.1 g of cyclohexanol admixed with 1.1% of cyclohexanone, 11 g of a mixture of 1-cyclohexylidene-2-cyclohexanone and 1-cyclohexenyl-2-cyclohexanol, and 13.9 g of trimeric products.

Reaction of diisobutylisopropoxyaluminum with cyclohexanone. Into 37 g of diisobutylisopropoxyaluminum in 35 ml of anhydrous toluene was stirred 28.4 g of cyclohexanone with heating to 90-100° and with simultaneous distillation of the 49-75° fraction. After the whole of the cyclohexanone had been added, heating was carried out for 20 min at 105-110°. There was collected 20.25 g of gas (together with liquid residue) containing 3.5% isobutylene and 96.5% isobutane. After the gas had gone off, the trap retained 2.1 g liquid residue. Fractional distillation of the latter and of the 49-75° fraction gave 2.25 g of acetone. The usual decomposition of the reaction mixture and distillation of the toluene gave a product which was distilled to give 8.9 g of cyclohexanol, 15.1 g of a mixture of dimeric products, and 3.2 g of trimeric products.

Reaction of triisobutylaluminum with 3 moles of 4-methylcyclohexanone. To 32.5 g (0.16 mole) of triisobutylaluminum was added 16.8 g (0.15 mole) of 4-methylcyclohexanone dropwise with vigorous stirring; towards the end of the operation the temperature had risen spontaneously to 60°. Heating for 40 min at 78-80° led to collection of 7.5 g of gas containing 78% isobutylene and 22% isobutane. To the solidified reaction mass was added 33.6 g (0.30 mole) of 4-methylcyclohexanone at 70-80°; towards the end of the addition the mass was heated for 40 min at 100°. In the trap was collected 18.6 g of gas containing 14.5% isobutylene and 85.5% isobutane. The reaction mass was dissolved in 75 ml of dry ether and decomposed in the usual manner. The ether was taken off and the residue distilled to give 8 g of 4-methylcyclohexanol with an admixture of 3% 4-methylcyclohexanone with b.p. 82-83° (20 mm), n^{20}_D 1.4584; 21 g of a mixture of dimeric products with b.p. 121-123° (4 mm), n^{20}_D 1.4973 [evidently a mixture of 1-methyl-3-(4-methylcyclohexylidene)-4-cyclohexanone and 1-methyl-3-(4-methylcyclohexenyl)-4-cyclohexanol], and 18.3 g of a mixture of trimeric products.

Hydrogenation of 12 g of the mixture of dimeric products was effected over 2 g of $Pd/BaSO_4$ in 50 ml of alcohol and 0.8 ml of glacial acetic acid. The catalyst was removed by filtration and the alcohol distilled in vacuo. Distillation of the residue gave 8.6 g of a mixture of 1-methyl-3-(4-methylcyclohexyl)-4-cyclohexanone and 1-methyl-3-(4-methylcyclohexyl)-4-cyclohexanol with b.p. 122-124° (3 mm), n^{20}_D 1.4865, d_4^{20} 0.9525.

To 8.6 g of this mixture in 25 ml of acetic acid was added a solution of 3 g of chromic acid in 25 ml of acetic acid and 3 ml of water at such a rate that a moderate amount of heat was released. The mass was then heated for 15 min to 50° and water was added; the oil was extracted with ether, washed with water, and dried over sodium sulfate. The ether was taken off in vacuo and 6.2 g of 1-methyl-3-(4-methylcyclohexyl)-4-cyclohexanone was obtained:

B.p. 93-95° (1 mm), $n^{22.5}_D$ 1.4821, d_4^{20} 0.9520.

Oxime: m.p. 123-124° (from alcohol).

Literature data [7]: n^{24}_D 1.4852, d_4^{24} 0.947; m.p. 123-124°.

Reaction of triisobutylaluminum with 3 moles of cyclopentanone. To 53 g (0.26 mole) of triisobutylaluminum was added 21.9 g (0.26 mole) of cyclopentanone dropwise with vigorous stirring; during this operation the temperature rose to 70°. In the trap was collected 13.7 g of gas containing 85% isobutylene and 15% isobutane.

To the solidified product was added 43.8 g (0.52 mole) of cyclopentanone while heating to 60-70°; in the course of the addition the reaction went very irregularly and the temperature rose spontaneously to 120°; the remaining quantity of cyclopentanone was added at 100-120°. In the trap was collected 28.2 g of gas containing 21% isobutylene and 79% isobutane.

To the reaction mixture was added 100 ml of absolute ether, and decomposition was effected in the usual manner. The ether was taken off and the residue distilled to give 8.2 g of cyclopentanol (containing 2% cyclopentanone), 38.6 g of a mixture of dimeric and trimeric products, and a residue in the flask of 8.3 g.

Hydrogenation of 19.8 g of the mixture of dimeric and trimeric products was effected over 2.5 g of $Pd/BaSO_4$ in 50 ml of alcohol and 1 ml of glacial acetic acid. After removal of the catalyst and the alcohol, the residue was distilled in vacuo. There were obtained 5.2 g of a mixture of 28% 1-cyclopentyl-2-cyclopentanol and 72% 1-cyclopentyl-2-cyclopentanone with n^{20}_D 1.4805 [2,4-dinitrophenylhydrazone m.p. 157-158°; literature [8]: m.p. 158-159°]

and 12 g of a fraction with b.p. 120-125° (2 mm). The latter was mainly a mixture of trimeric condensation products.

Interaction of diisobutylaluminum chloride with 1 mole of cyclohexanone. To 25.8 g (0.14 mole) of diisobutylaluminum chloride was added 12.74 g (0.13 mole) of cyclohexanone with vigorous stirring initially at room temperature. The temperature immediately rose to 40°. The main quantity of cyclohexanone was added at 50-60°, and towards the end the temperature was 70°. After 30 minutes' heating the amount of gas collected was 6.8 g, containing 92.5% isobutylene and 7.5% isobutane. The usual decomposition of the reaction mixture and removal of the ether was followed by distillation to give 8.7 g of cyclohexanol.

SUMMARY

It was shown that reaction of triisobutylaluminum with cyclohexanone, 4-methylcyclohexanone, and cyclopentanone takes the form, apart from reduction, of condensation under the action of the resulting diisobutylalkoxyaluminum.

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SOME UNSYMMETRICAL DERIVATIVES OF ALKYL-PHOSPHINIC ACIDS

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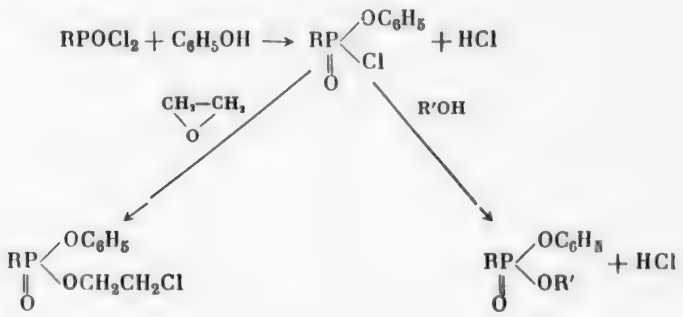
Symmetrical derivatives of monoalkyl- and monoarylphosphinic acids (dichlorides, diamides, diesters) are widely known [1]. Very much less attention has been paid to the corresponding unsymmetrical compounds, although they are also of interest on account of their specific properties which are governed by the unsymmetrical structure of their molecules and the differing strengths of their chemical bonds.

This paper contains an account of the preparation of some previously unknown derivatives (ester-chlorides and unsymmetrical esters containing one or two aryl groups) of methyl-, chloromethyl-, and β-chloroethylphosphinic acids.

Ester-chlorides (see table , 1-3) were synthesized by reaction of equimolecular quantities of dichlorides of the corresponding phosphinic acids with phenol and subsequent fractionation of the resulting substances. Interaction of ester-chlorides with some hydroxyl-containing aromatic compounds, ethanol, and ethylene oxide gave unsymmetrical esters of methyl-, chloromethyl-, and β-chloroethylphosphinic acids (see table, 4-9).

All the synthesized compounds are liquids. The full aryl esters of methylphosphinic acid are less mobile than the ester-chlorides and the alkaryl esters. The product of reaction of the phenyl ester of methylphosphinic chloride with methyl salicylate was so viscous that its specific gravity could not be determined.

The above transformations can be represented as follows:



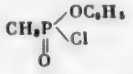
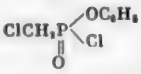
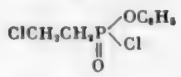
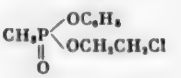
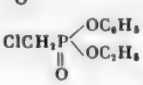
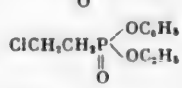
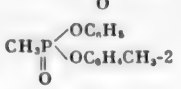
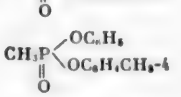
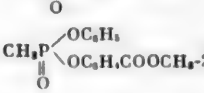
EXPERIMENTAL*

Phenyl ester of methylphosphinic chloride (I). Into a flask fitted with reflux condenser + calcium chloride tube, stirrer, and thermometer were charged 133 g of methylphosphinic chloride and 94 g of phenol. The mixture was stirred and heated at 120° for 2 hr, and then at 140° for 2 hr until substantially no more hydrogen chloride came off. The reaction product (a dark liquid) was distilled in vacuo. The 100-130° (2 mm) fraction was slowly fractionated in vacuo. Yield 101 g.

Found %: P 16.1; Cl 18.5. $C_7H_8O_2PCl$. Calculated %: P 16.26; Cl 18.6.

A colorless, transparent liquid, soluble in benzene, toluene, and ether. It reacts with water and alcohol with heat development and evolution of hydrogen chloride.

* N. I. Bondar' participated in the experimental work.

Serial No	Formula	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Yield (in %)
1		114° (2)	1.5223	1.2829	45.32	45.38	53
2		123—124 (1)	1.5354	1.3989	50.12	50.25	50
3		130—132 (1)	1.5329	1.3528	54.83	54.86	50
4		138—139 (1)	1.5113	1.2570	55.94	55.89	79.5
5		140 (1)	1.5082	1.2557	55.72	55.89	80
6		161 (1.5 — 2)	1.5048	1.2176	60.55	60.51	62.5
7		188—190 (1.5—2)	1.5455	1.1723	70.78	70.52	58
8		186—188 (1.5—2)	1.5454	1.1727	70.74	70.52	73
9		207—210 (1.5—2)	1.5463	*	—	—	60

* The liquid was so viscous that its specific gravity could not be determined.

Benzyl esters of chloromethyl- and β-chloroethylphosphinic chlorides (2 and 3) were similarly prepared from the dichlorides [2] of chloromethyl- and β-chloroethylphosphinic chlorides and phenol.

Found %: P 13.62; Cl (hydrolyzable [3]) 15.6. $C_7H_7O_2PCl_2$. Calculated %: P 13.77; Cl (hydrolyzable) 15.75.

Found %: P 12.8; Cl (hydrolyzable [3]) 14.9. $C_8H_9O_2PCl_2$. Calculated %: P 12.8; Cl (hydrolyzable) 14.83.

Phenyl β-chloroethyl ester of methylphosphinic acid (4). Dry ethylene oxide was passed through a stirred mixture of 78 g of ester-chloride (1) and 0.5 g of aluminum chloride until the exothermic reaction ceased. The temperature was held at 10-20° by external cooling. The catalyst was filtered off, and the filtrate distilled in vacuo. Yield 77 g.

Found %: P 13.12; Cl 15.02. $C_9H_{12}O_3PCl$. Calculated %: P 13.20; Cl 15.11.

A colorless, transparent liquid, soluble in alcohol, ether, benzene, and toluene; insoluble in water. All the remaining esters (5-9) have the same properties.

Phenyl ethyl ester of chloromethylphosphinic acid (5). To 25 g of dry alcohol, stirred and externally cooled was gradually added 60 g of ester-chloride (2). Reaction temperature about 0°. The evolved hydrogen chloride and excess alcohol were distilled from the reaction mixture at 10-20 mm residual pressure and room temperature. The residue was neutralized with sodium carbonate solution and immediately distilled in vacuo. Yield 50 g.

Found %: P 13.05; Cl 14.95. $C_9H_{12}O_3PCl$. Calculated %: P 13.20; Cl 15.11.

Phenyl ethyl ester of β-chloroethylphosphinic acid (6). Similarly prepared from ester-chloride (3) and ethanol.

Found %: P 12.31; Cl 14.11. $C_{10}H_{14}O_3PCl$. Calculated %: P 12.46; Cl 14.26.

Phenyl o-cresyl ester of methylphosphinic acid (7). A mixture of 19 g of ester-chloride (1) and 12 g of o-cresol was stirred and heated for 4 hr at 170° until evolution of hydrogen chloride had substantially ceased. Still

unremoved hydrogen chloride and the excess of o-cresol were distilled from the reaction mixture, and the residue was distilled in vacuo. Yield 15.2 g.

Found %: C 63.3; H 5.91; P 11.61. $C_{14}H_{15}O_3P$. Calculated %: C 64.1; H 5.77; P 11.81.

Phenyl p-cresyl ester of methylphosphinic acid (8). Similarly prepared from ester-chloride (1) and p-cresol.

Found %: C 63.6; H 5.81; P 11.72. $C_{14}H_{15}O_3P$. Calculated %: C 64.1; H 5.77; P 11.81.

Reaction of phenyl ester of methylphosphinic chloride with methyl salicylate (9). Into a mixture of 16 g of methyl salicylate, 8 g of pyridine, and 30 ml of benzene at room temperature was stirred 19 g of ester-chloride (1). The reaction mixture was then heated to 30-35° for an hour, and the precipitated pyridine hydrochloride was filtered off and washed with benzene. The solvent was driven off from the filtrate, and the residue twice distilled in vacuo. Yield 18.3 g.

Found %: C 58.2; H 5.2; P 9.98. $C_{15}H_{15}O_5P$. Calculated %: C 58.8; H 4.95; P 10.12.

SUMMARY

Several previously unknown unsymmetrical derivatives of methyl-, chloromethyl-, and β-chloroethylphosphinic acids were synthesized, and their properties described.

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THE CHEMISTRY OF UNSATURATED ETHERS

VII. ADDITION OF THE ACETAL OF β-C_{14}-ALDEHYDE TO 1-ETHOXY--METHYL-1,3-BUTADIENE. A NEW SYNTHESIS OF β-C_{19}-ALDEHYDE

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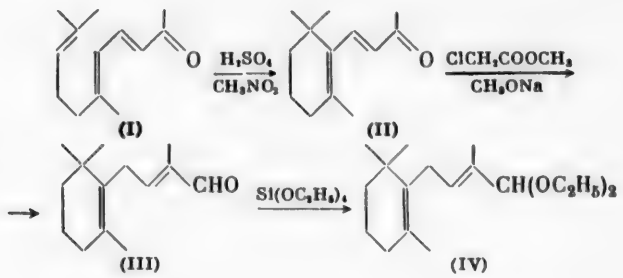
pp. 3319-3323, October, 1961
Original article submitted October 6, 1960

In the preceding communication it was shown that acetals of α, β-unsaturated aldehydes add on with facility to 1-ethoxy-2-methyl-1,3-butadiene in the 1,4-position to give a mixture of α,β-unsaturated ethoxyacetals which can then be converted into polyenic aldehydes [1]. Great interest is attached to the study of the addition of the acetal of β-C_{14}-aldehyde to 1-ethoxy-2-methyl-1,3-butadiene and to the realization of the synthesis of β-C_{19}-aldehyde.

β-C_{19}-Aldehyde or 8-(2',6',6'-trimethylcyclohexen-1'-yl)-2,6-dimethyl-2,4,6-octatrien-1-al (X) is a key substance in the synthesis of crotinoids.

Condensation of two molecules of β-C_{19}-aldehyde with one molecule of acetylene (by the scheme $C_{19} + C_2 + C_{19} = C_{40}$) leads to C_{40}-diol from with β-carotin is easily obtained by dehydration and hydrogenation [2].

The diethylacetal of β-C_{14}-aldehyde (IV) needed for the reaction is synthesized from pseudoionone by the following steps:



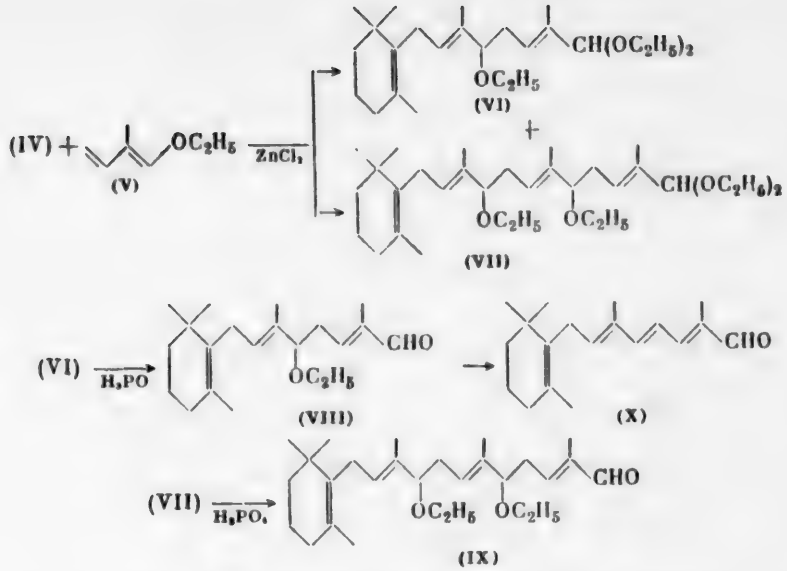
Cyclization of pseudoionone (I) to β-ionone (II) was effected with the help of 100% sulfuric acid in a medium of nitromethane [3]. β-C_{14}-Aldehyde (III), prepared by the Darzans method from β-ionone (II) and methyl chloroacetate [4], was converted into acetal (IV) with the help of tetraethoxysilane [5].

Addition of the diethylacetal of β-C_{14}-aldehyde (IV) to 1-ethoxy-2-methyl-1,3-butadiene (V) was carried out at 45° in presence of 10% zinc chloride solution. Formation of products of further addition of the alkoxydiene (V) was minimized by use in the reaction of a two-fold excess of the acetal of β-C_{14}-aldehyde (IV) which was later recovered unchanged.

The reaction led to isolation of the β-C_{19}-ethoxyacetal (VI) in a yield of 42%, and of β-C_{24}-diethoxyacetal (VII) in a yield of 16%.

Treatment of the ethoxyacetals with dilute phosphoric acid led to quantitative conversion into β-C_{19}-ethoxyaldehyde (VII) and β-C_{24}-diethoxyaldehyde (IX) respectively.

The ultraviolet absorption spectra of ethoxyaldehydes (VIII) and (IX) (Fig. 1) possess a strong band in the 230 mμ region which is characteristic of α, β-unsaturated aldehydes [6]. This proves that addition of acetal (IV) to diene (V) proceeds in the 1,4-position.



Hydrolysis gives ethoxyaldehyde (VIII) in quantitative yield and in a sufficiently pure state; it can therefore be used without preliminary distillation.

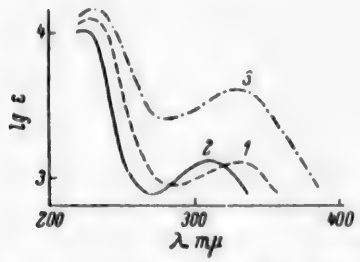


Fig. 1. Ultraviolet absorption spectra of β-C_{19}-ethoxyaldehyde (VIII). 1) λ_{max} (in alcohol) 229 mμ (ε 15300), 325 mμ (ε 1500); 2) λ_{max} (in heptane) 225 mμ (ε 11100), 314.5 mμ (ε 1600). Ultraviolet absorption spectrum of β-C_{24}-diethoxyaldehyde (IX). 3) λ_{max} (in alcohol) 232 mμ (ε 14800), 330 mμ (ε 4100).

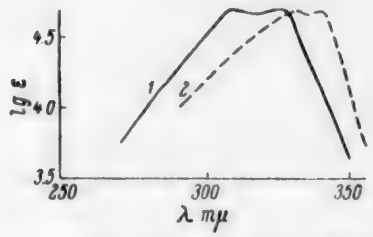


Fig. 2. Ultraviolet absorption spectrum β-C_{19}-aldehyde (X). 1) λ_{max} (in isooctane) 311.5 mμ (ε 47500), 323 mμ (ε 46500); 2) λ_{max} (in alcohol) 331 mμ (ε 43400), 337 mμ (ε 43000).

Heating of β-C_{19}-ethoxyaldehyde (VIII) in toluene solution in presence of p-toluenesulfonic acid gives crystalline, exclusively trans-β-C_{19}-aldehyde (X) with m.p. 64-65°.

β-C_{19}-Aldehyde was characterized as the 2,4-dinitrophenylhydrazone (m.p. 200°) and by its ultraviolet absorption spectrum (Fig. 2), which was identical with the spectrum of the β-C_{19}-aldehyde reported in the literature for use in preparation of biologically active β-carotin [2].

The infrared absorption spectrum confirmed the presence of an α, β, γ, δ-unsaturated CO group and of the trans-conjugated double bond (absorption bands 1682, 1608, 1465, 1407, 1385, 1363, 1287, 1275, 1194, 1112, 1005, 965, 850, 835, 825, 675 cm^{-1} [7] (Fig. 3).

EXPERIMENTAL

Pesudoionone (I) after purification through the bisulfite compound had b.p. 115-118° at 2 mm, n^{20}_D 1.5319, λ_{max} (in alcohol) 291 mμ (ε 21000).

β-Ionone (II). A four-necked flask, fitted with mechanical stirrer, thermometer, dropping funnel, and reflux condenser + calcium chloride tube, was charged with 1000 g of dry, freshly distilled nitromethane. At −30° 750 ml

of 100% sulfuric acid was added in the course of 10 min, and then at the same temperature 500 g of pseudoionone was added in the course of 25 min. It was necessary to keep the temperature of the reaction mixture not higher than −25°. The cooling medium was removed and the temperature rose to +10° in the course of 45 min. At this temperature the mixture was vigorously stirred for 4.5 min and then poured onto 1.5 kg of crushed ice and 1500 ml of benzene. The upper layer was separated and the lower one extracted with benzene. The combined benzene solution was washed with water (900 ml), 5% sodium bicarbonate solution, and again with water. The solvent was removed in a low vacuum, and the residue distilled. Yield 378 g (78%).

B.p. 80° at 0.07 mm, n^{20}_D 1.5181, λ_{max} (in alcohol) 221.5 mμ (ε 7000), 296.5 mμ (ε 10300).

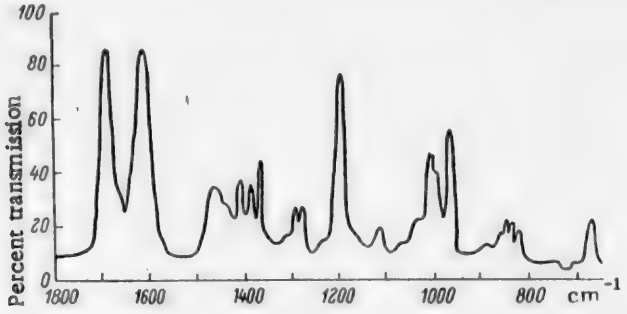


Fig. 3. Infrared absorption spectrum of a 9.45% solution of β-C_{19}-aldehyde in carbon tetrachloride.

β-C_{14}-Aldehyde (III) was prepared by the earlier procedure [4] and then purified by crystallization from isopentane at −70°.

n^{20}_D 1.5095, λ_{max} (in alcohol) 234 mμ (ε 15700), λ_{max} (in isooctane) 224 mμ (17000), 280 mμ (ε 600).

Diethylacetal of β-C_{14}-aldehyde (IV). A mixture of 3.75 g of purified crystalline β-C_{14}-aldehyde, 0.3 ml of anhydrous ethanol, 0.2 ml of 87% phosphoric acid, and 4.1 g of tetraethoxysilane was allowed to stand for five days. The reaction mass was then diluted with anhydrous ether and shaken for 15 min with 10 ml of 10% sodium hydroxide solution. The ethereal layer was separated, washed twice with water, dried, and distilled. Yield 4.0 g (83%).

B.p. 95-97° at 0.05 mm, n^{20}_D 1.4785.

Addition of diethylacetal of β-C_{14}-aldehyde (IV) to 1-ethoxy-2-methyl-1,3-butadiene (V). A four-necked flask, equipped with mechanical stirrer, thermometer, lead-in tube for nitrogen, dropping funnel, and reflux condenser + drying tube, was charged with 20 ml of 10% solution of zinc chloride in ethyl acetate. Addition was then made with stirring of 180° of diethylacetal of β-C_{14}-aldehyde, followed over a period of 4.5 hr (with vigorous stirring) at 50° by 38.2 g of 1-ethoxy-2-methyl-1,3-butadiene. The reaction mass was stirred at this temperature for a further 8 hr. It was then neutralized with sodium ethoxide, diluted with ether, washed with water, and dried with magnesium sulfate. Two distillations in vacuo gave three fractions:

1st fraction: 85.5 g of initial acetal of β-C_{14}-aldehyde (IV) with b.p. 90-108° at 0.05 mm, n^{20}_D 1.4830.

2nd fraction: 56 g (42%) of 8-(2',6',6'-trimethyl-1'-cyclohexenyl)-1,1,5-triethoxy-2,6-dimethyl-2,6-octadiene (VI) with b.p. 132-134° at 0.035 mm, n^{20}_D 1.4940.

Found %: C 76.76, 76.31; H 10.83, 10.98. $C_{25}H_{44}O_3$. Calculated %: C 76.48; H 11.30.

3rd fraction: 13.8 g (16%) of 12-(2',6',6'-trimethylcyclohexen-1'-yl)-1,1,5,9-tetraethoxy-2,6,10-trimethyl-2,6,10-dodecatriene (VII) with b.p. 170-171° at 0.05 mm, n^{20}_D 1.5028.

Found %: C 76.51, 76.21; H 10.83, 11.20. $C_{32}H_{56}O_4$. Calculated %: C 76.14; H 11.18.

β-C_{19}-Ethoxyaldehyde (VIII). A mixture of 34.8 g of β-C_{19}-ethoxyacetal (VI), 20 ml of 10% phosphoric acid, and 50 ml of alcohol was stirred at the boil in a nitrogen atmosphere for an hour. The reaction product was extracted with ether, washed with water, with 5% sodium bicarbonate solution, again with water, and dried with magnesium sulfate. Distillation in vacuo in a stream of dry nitrogen gave 30.8 g of 8-(2',6',6'-trimethylcyclohexen-1'-yl)-5-ethoxy-2,6-dimethyl-2,6-octadien-1-al (VIII) with b.p. 127-130° at 0.06 mm, n^{20}_D 1.5067.

Found %: C 79.43, 79.53; H 10.17, 10.22. $C_{21}H_{34}O_2$. Calculated %: C 79.19; H 10.76.

2,4-Dinitrophenylhydrazone: m.p. 129°.

Found %: N 10.96, 11.53. $C_{27}H_{38}O_5N_4$. Calculated %: N 11.24.

β-C_{24}-Diethoxyaldehyde (IX). A mixture of 5.4 g of β-C_{24}-diethoxyacetal (VII), 20 ml of dioxane, and 6 ml of 10% phosphoric acid was stirred at 65° in a nitrogen atmosphere for 2.5 hr. The usual working-up and vacuum distillation gave 4.85 g of 12-(2',6',6'-trimethylcyclohexen-1'-yl)-5,9-diethoxy-2,6,10-trimethyl-2,6,10-dodecatrienal (IX) with b.p. 158-162° at 0.01 mm, n^{20}_D 1.5120.

Found %: C 78.03, 78.26; H 11.00, 10.75. $C_{28}H_{46}O_3$. Calculated %: C 78.09; H 10.77.

2,4-Dinitrophenylhydrazone: m.p. 96°.

β-C_{19}-Aldehyde (X). A Favorskii flask with a dephlegmator (30 cm) equipped with a nitrogen lead-in tube and dropping funnel, was charged with 4.8 g of β-C_{19}-ethoxyaldehyde (VIII), 150 ml of anhydrous toluene, and 0.1 g of p-toluenesulfonic acid. The mixture was heated in a nitrogen atmosphere in presence of a trace of hydroquinone at a bath temperature of 135°. With progressive distillation of the azeotropic mixture of toluene and alcohol (vapor temperature 100-105°), anhydrous toluene was added to the flask at such a speed that the volume of reaction mass remained constant. After 3.5 hr a total of 135 ml of distillate had been taken off, and the distillate no longer contained alcohol (test for active carbon by the Chugaev – Tserevitinov method). After cooling, the reaction product was diluted with ether, washed with 5% sodium bicarbonate solution and with water, dried with magnesium sulfate, and distilled in vacuo in a stream of dry nitrogen. Yield 2.8 g (67%). B.p. 139-142° at 0.07 mm, m.p. 64-65° (from alcohol), n^{20}_D 1.5800; stout, yellow crystals.

2,4-Dinitrophenylhydrazone: m.p. 199-200°, λ_{max} (in isooctane) 396 mμ.

Found %: N 12.51, 12.30. $C_{25}H_{32}O_4N_4$. Calculated %: N 12.38.

SUMMARY

1. The addition of the acetal of β-C_{14}-aldehyde to 1-ethoxy-2-methyl-1,3-butadiene was studied.

2. β-C_{19}-Ethoxyaldehyde, 8-(2',6',6'-trimethylcyclohexen-1'-yl)-5-ethoxy-2,6-dimethyl-2,6-octadien-1-al, and β-C_{24}-diethoxyaldehyde, 12-(2',6',6'-trimethylcyclohexen-1'-yl)-5,9-diethoxy-2,6,10-trimethyl-2,6,10-dodecatrien-1-al were prepared and can be used as intermediates in the synthesis of carotinoids.

3. A new method is proposed for the preparation of fully trans-β-C_{19}-aldehyde from which β-carotin can be prepared by well-known methods.

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CONFIGURATION AND PROPERTIES OF UNSATURATED ACIDS AND THEIR DERIVATIVES

XIV. PROPERTIES OF ESTERS OF CIS- AND TRANS-PETROSELINIC ACIDS

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It is well known that the configuration of cis- and trans-petroselinic acids $CH_3(CH_2)_{10}CH = CH(CH_2)_4COOH$ and some of their esters affects the physical and chemical properties of these substances [1]. The cis forms have been found to be more active in reactions of oxidation by potassium permanganate and benzoyl hydroperoxide than the corresponding trans forms.

Since the effect of the alcohol radical in oxidation of the esters showed up rather clearly in these experiments, it became entirely evident that further study of this fact was needed in the case of a series of different esters of petroselinic acids.

The methyl, propyl, isopropyl, benzyl, and phenyl esters of petroselinic acids were selected for investigation of the oxidation by benzoyl hydroperoxide, and the methyl, propyl, isopropyl, phenyl, benzyl, and triphenylmethyl esters for the reaction of saponification.

The results of the oxidation experiments showed that the esters of petroselinic acid (cis form) are more active in comparison with the esters of petroselaidic acid (trans form). In the saponification experiments, on the contrary, the trans forms are more active in comparison with the cis forms. In all cases an effect is manifested for the alcohol radical, being more marked for the trans form in oxidation and for the cis form in saponification. These data agree with the concepts of steric hindrance and with the facts obtained in studying analogous reactions of other monounsaturated acids and their derivatives [2].

Recently, in explaining steric hindrances in esterification and ester hydrolysis reactions, the "rule of six" [3] is often used; this rule was developed for application to saturated acids and their derivatives. It was of interest to study the possibility of applying this rule to the case in question. In petroselinic acids and their esters both the radical $-(CH_2)_4COOR$ and the radical $-(CH_2)_{10}CH_3$ are capable of forming coiled chains. In view of the absence of any difference of the sixth places in these chains for the cis and trans forms, evidently the effect of these chains on the reactivity is connected with their differing location relative to the double bond. If the presence of two coiled chains in the indicated esters is assumed, then it is clear that the blocking of the space around the ethylene double bond will be considerably greater in the case of the trans form. At the same time, the space at the carboxyl evidently is blocked to a greater degree in the case of the cis form, in this case the effect of the alcohol radical being expected to be the most clearly visible. Hence, it follows that reactions at the site of the double bond should take place more readily for the cis form, but reactions at the carboxyl group for the trans form, as is confirmed by the experiments.

The attempt to apply the "rule of six" for explaining the differing activity of the cis and trans forms of derivatives of petroselinic acids is a development of views on the effect of configuration on the properties of unsaturated acids [4].

EXPERIMENTAL

Petroselinic and petroselaidic acids and their methyl, propyl, and benzyl esters were prepared as described previously [1]; their properties corresponded to those reported in the literature.

TABLE 1. Effect of Nature of Alcohol Radical on Saponification Rate of Esters of cis- and trans-Petroselinic Acids

Alcohol radical	$K_{17°} \cdot 10^5$, cis acid	$K_{17°} \cdot 10^5$ trans acid
Methyl	108	127
Propyl	108	127
Isopropyl	89	119
Phenyl	83	130
Benzyl	75	109
Triphenylmethyl	11	111

TABLE 2. Effect of Nature of Alcohol Radical on Oxidiation Rate of Esters of cis- and trans-Petroselinic Acids

Alcohol radical	$K_{16°} \cdot 10^5$, cis acid	$K_{16°} \cdot 10^5$ trans acid
Methyl	256	156
Propyl	235	140
Isopropyl	229	130
Phenyl	220	126
Benzyl	222	129

Isopropyl petroselinate was prepared by esterification of petroselinic acid with isopropanol in the presence of concentrated sulfuric acid, heating 4 hr on a steam bath. Colorless liquid; b.p. 192° (6 mm), n^{20}_D 1.4480, saponification number 173, calcd. 172.8.

Isopropyl petroselaidate was prepared from the silver salt of the acid and isopropyl bromide. B.p. 206° (7 mm), n^{20}_D 1.4487, saponification number 173, calcd. 172.8.

Phenyl petroselinate was prepared from petroselinyl chloride and potassium phenolate in benzene solution, heating 28 hr on a steam bath. B.p. 222° (5 mm), n^{48}_D 1.4681, acid number 0.

Phenyl petroselaidate was prepared analogously. B.p. 209° (5 mm), n^{48}_D 1.4690, acid number 0.

Triphenylmethyl petroselinate was prepared from the potassium salt and triphenylchloromethane in dry benzene by heating 28 hr on a steam bath. M.p. 78° (from alcohol), saponification number 107, calcd. 106.8.

Triphenylmethyl petroselaidate was prepared analogously. M.p. 98° (from alcohol), saponification number 107, calcd. 106.8.

Saponification of the esters was carried out at 17° with 0.01 N alcoholic KOH solution. A solution of 1/2000 mole of the ester in 20 ml of alcohol was mixed with 50 ml of the caustic solution, and the time of reaction was taken starting at this moment. Samples were withdrawn at definite time intervals and titrated to determine the residual alkali quantity. The reaction rate constants for the saponification were calculated according to a bimolecular reaction equation. For the phenyl esters, account was taken of the double consumption of alkali (Table 1).

Oxidation of esters. The oxidation of equimolar quantities of the esters was accomplished in anhydrous acetone by benzoyl hydroperoxide (0.05 N), prepared according to literature data [5]. In each experiment, 10 ml of the acetone solution of the ester was mixed with 10 ml of the benzoyl hydroperoxide solution at 16°. The content of active oxygen was determined iodometrically. The reaction rate constants for the oxidation were calculated according to a bimolecular reaction equation (Table 2).

SUMMARY

1. It has been established that geometric isomers of esters of petroselinic and petroselaidic acids show differing reactivity in saponification and in oxidation by benzoyl hydroperoxide. The cis form is less active than the trans form in saponification; in oxidation, on the contrary, the trans form is the less active. The size of the alcohol radicals in the esters has a marked effect on the activity of the esters.

2. Isopropyl petroselinate, isopropyl petroselaidate, phenyl petroselinate, phenyl petroselaidate, triphenylmethyl petroselinate, and triphenylmethyl petroselaidate have been synthesized for the first time.

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SYNTHESIS AND CERTAIN REACTIONS OF NITRILES OF N,N-DI(2-CHLOROETHYL)AMINOPHENYLALKANOIC ACIDS

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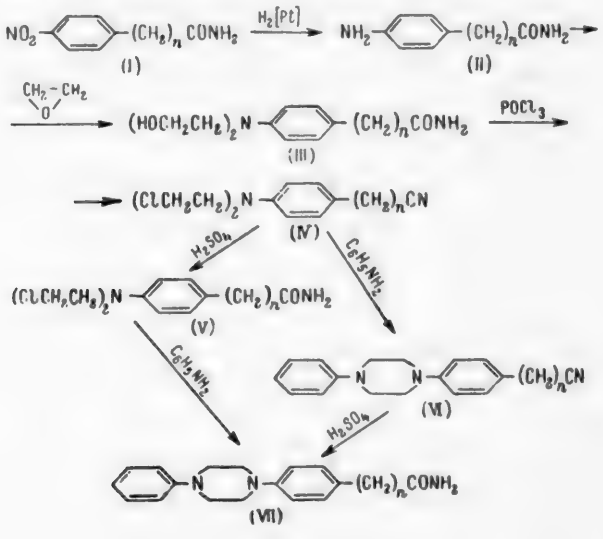
It is known [1] that the nitriles of p-[di(2-chloroethyl)amino]phenylalkanoic acids (IV) can be used for the synthesis of compounds possessing antitumor activity. However, p-[di(2-chloroethyl)amino]benzonitrile cannot be synthesized by the proposed method [1].

In the present work it is established that the synthesis of p-[di(2-chloroethyl)amino]benzonitrile (IV; n = 0) can be accomplished readily by replacing the p-aminobenzonitrile by p-aminobenzamide (II; n = 0). The latter reacts readily with ethylene oxide and gives p-[di(ethylol-2)amino]benzamide (III; n = 0) with high yield. The structure of the compound obtained is proven by the fact that on heating with phosphoryl chloride it is converted to the known p-[di(2-chloroethyl)amino]benzonitrile (IV; n = 0), synthesized by a more complex scheme from aniline through p-[di(2-chloroethyl)amino]benzaldehyde [1].

p-Aminophenylacetamide (II; n = 1) also enters into reaction with ethylene oxide more readily than the corresponding nitrile; however, the difference in reaction rate here is less marked. Thereby there is obtained p-[di(ethylol-2)amino]phenylacetamide (III; n = 1), which on interaction with phosphoryl chloride gives p-[di(2-chloroethyl)amino]-phenylacetonitrile (IV; n = 1).

The initial amides were obtained by catalytic reduction of the corresponding nitro compounds. This method under laboratory conditions proved to be considerably less laborious than the reduction with ammonium sulfide described in the literature [2-4] and other methods of preparation [5-6].



The resulting chloroethylaminonitriles (IV) are converted readily to the corresponding amides (V) by moderate heating in concentrated sulfuric acid. On complete hydrolysis of (IV) by concentrated hydrochloric acid, the corresponding acids are formed. On interaction with aniline, the p-[di(2-chloroethyl)amino]phenylacetonitrile and the p-[di(2-chloroethyl)amino]phenylacetamide give the corresponding derivatives of diphenylpiperazine (VI and VII, n = 1). The reaction of p-[di(2-chloroethyl)amino]benzamide with aniline takes place with more difficulty, and a considerable part of the amide (IV, n = 0) remains unreacted; under the same conditions, p-[di(2-chloroethyl)amino]-benzonitrile does not react at all with aniline.

The results of investigations of the toxicity and antitumor activity of some of the compounds synthesized were published in the works of S. Keblas and V. Kutorga [7].

EXPERIMENTAL

p-Aminobenzamide (II, n = 0). A 16.6 g quantity (0.1 g-mole) of p-nitrobenzamide, 140 ml alcohol, and 0.2 g platinic oxide (according to Adams) were shaken in a hydrogen atmosphere. After the absorption of 6.75 liters (0.3 g-mole) of hydrogen, the reaction mixture was heated until the precipitated p-aminobenzamide was dissolved, and the catalyst was filtered out. Part of the alcohol was distilled from the filtrate, and the material obtained was recrystallized. Yield 11.6 g (85%); m.p. 181-181.5° (from water). Literature data: m.p. 178-179° [2, 5], 182.9 (corrected) [4]. A mixed sample with a preparation synthesized according to literature data [2] did not give any melting point depression.

p-[di(Ethylol-2)amino]benzamide (III, n = 0). A mixture of 6.8 g (0.05 g-mole) of p-aminobenzamide with 10 ml ethylene oxide and 10 ml of 10% acetic acid was allowed to stand 48 hr at room temperature. So long as the solution did not become homogeneous, it is recommended that the reaction mixture be shaken periodically. The crystals were filtered off by vacuum and washed with a small amount of cold water. Yield 10 g (90%). White lustrous crystals with m.p. 175-176° (from water).

Found %: C 58.64; H 7.28; N 12.47. $C_{11}H_{16}O_3N_2$. Calculated %: C 58.91; H 7.19; N 12.49.

Readily soluble in hot water, alcohol, acetone; little soluble in nonpolar organic solvents.

p-[di(2-Chloroethyl)amino]benzonitrile (IV, n = 0). A 4.6 g quantity of p-[di(ethylol-2)amino]benzamide (III, n = 0) and 12 ml of freshly distilled phosphoryl chloride were heated 1 hr with a reflux condenser in a water bath (75-90°). The excess phosphoryl chloride was decomposed by pouring the chilled reaction mixture into ice water, and the recovery of the reaction product was carried out, in a manner analogous to that described in [1]. Yield 3.5 g (71%), m.p. 89-90° (from alcohol). A mixed sample with the nitrile synthesized from p-[di(2-chloroethyl)amino]benzaldehyde [1] did not show any melting point depression.

A 3 g quantity of the nitrile was hydrolyzed by boiling with 60 ml of concentrated hydrochloric acid. Obtained 2.7 g (95%) of p-[di(2-chloroethyl)amino]benzoic acid with m.p. 168° (from benzene). Literature data: m.p. 171.5° [8], 168-169° [9].

A 4 g quantity of the well-pulverized nitrile was heated in 20 ml of concentrated sulfuric acid at 65-75° for 2 hr. Then the cooled solution was poured onto ice. Obtained 2.7 g (62%) of p-[di(2-chloroethyl)amino]benzamide (V, n = 0) with m.p. 124-126°, identical to the amide synthesized [10] by another method.

p-Aminophenylacetamide (II, n = 1). A 10.5 g quantity of p-nitrophenylacetamide in 140 ml of alcohol was reduced with hydrogen in the presence of platinum catalyst (according to Adams). Yield 7 g (80%), m.p. 156-157° (from alcohol). Literature data: m.p. 153-154° [3], 161-162° (corrected) [6].

p-[di(Ethylol-2-)amino]phenylacetamide (III, n = 1). A mixture of 4.9 g of p-aminophenylacetamide with 5.3 ml ethylene oxide and 5.3 ml 10% acetic acid was allowed to stand 24 hr at room temperature. The resulting dark homogeneous solution, on rubbing with a glass rod and cooling, solidified to a crystalline mass; the crystals were filtered off by suction and dried. Yield 7 g (90%), m.p. 122-123° (from water). Readily soluble in water, alcohol.

Found %: C 60.26, 60.20; H 7.60, 7.58; N 11.74, 11.64. $C_{12}H_{18}O_3N_2$. Calculated %: C 60.49; H 7.60; N 11.71.

p-[di(2-Chloroethyl)amino]phenylacetonitrile (IV, n = 1). The reaction of p-[di(ethylol-2)amino]phenylacetamide (1 g) with phosphoryl chloride (3 ml) was carried out analogously. Yield 0.7 g (65%); m.p. 46-47° (from ether). A mixed sample with a preparation obtained according to literature data [1] did not show any melting point depression.

On boiling 1 g of the nitrile in 5 ml of concentrated hydrochloric acid with subsequent neutralization with potassium bicarbonate until the resulting acid was completely precipitated, there was obtained 0.98 g (91%) of p-[di(2-chloroethyl)amino]phenylacetic acid with m.p. 103-104° (from benzene with petroleum ether), identical to a preparation synthesized according to literature data [11].

On heating 5 g of the nitrile in 15 ml of concentrated sulfuric acid at 50° for 1 hr, there was obtained 4.8 g (91.8%) of p-[di(2-chloroethyl)amino]phenylacetamide (V, n = 1) with m.p. 123° (from benzene), identical to the amide synthesized previously [1].

p-(1-Phenylpiperazinyl-4)phenylacetonitrile (VI, n = 1). To a solution of 0.514 g (0.002 g-mole) of p-[di(2-chloroethyl)amino]phenylacetonitrile (IV, n = 1) in 40 ml of acetone, there was added 0.56 g (0.006 g-mole) of aniline and 40 ml of water. The reaction mixture was refluxed 3 hr. The following day, the precipitated crystals were filtered off by suction and recrystallized. Yield 280 mg (50.5%) with m.p. 145.5° (from alcohol).

Found %: C 78.01, 77.98; H 7.01, 6.71; N 15.16, 15.24. $C_{18}H_{19}N_3$. Calculated %: C 77.94; H 6.90; N 15.16.

p-(1-Phenylpiperazinyl-4)phenylacetamide (VII, n = 1). a) To a solution of 0.55 g (0.002 g-mole) of p-[di(2-chloroethyl)amino]phenylacetamide (V, n = 1) in 40 ml of acetone, there was added 0.56 g (0.006 g-mole) of aniline and 40 ml of water, and the resulting mixture was refluxed 3 hr. The reaction mixture on cooling precipitated 0.35 g (60%) of white lustrous crystals. M.p. 243-244° (from alcohol).

Found %: C 73.11, 73.08; H 7.16, 7.24; N 14.18, 14.23. $C_{18}H_{21}ON_3$. Calculated %: C 73.19; H 7.16; N 14.22.

b) A 277 mg quantity (0.001 g-mole) of p-(1-phenylpiperazinyl-4)phenylacetonitrile (VI, n = 1) was dissolved in 2 ml of concentrated sulfuric acid and heated 1 hr at 50-60°. Then the mixture was poured into ice water, and the resulting transparent solution was neutralized with 10% sodium carbonate solution. The free base (200 mg) was filtered off by suction and recrystallized.

p-(1-Phenylpiperazinyl-4)benzamide (VII, n = 0). A 1 g quantity of p-[di(2-chloroethyl)amino]benzamide (V, n = 0) was dissolved in 77 ml of acetone; 1.066 g of aniline and 77 ml of water were added, and the resulting mixture was refluxed 3 hr. The reaction mixture on cooling precipitated 150 mg of white lustrous crystals. After distilling off the acetone, 600 mg of a mixture of the reaction product and unreacted amide was precipitated. This mixture was separated into its constituent parts by extraction of the p-[di(2-chloroethyl)amino]benzamide with hot methanol. The methanol-insoluble material was removed by filtration and recrystallized from a large quantity of alcohol. Total yield 420 mg (42%). M.p. 265-268° (decompn.).

Found %: C 72.56, 72.16; H 6.61, 6.99; N 14.95, 14.88. $C_{17}H_{19}ON_3$. Calculated %: C 72.57; H 6.80; N 14.93.

From the methanol filtrate, by adding water, there was precipitated 120 mg of the initial p-[di(2-chloroethyl)-amino]benzamide with m.p. 122-124° (from aqueous methanol).

SUMMARY

1. A new method has been proposed for the preparation of p-[di(2-chloroethyl)amino]benzonitrile, suitable also for the synthesis of homologous nitriles.

2. A study has been made of the reaction of hydrolysis of the obtained di(2-chloroethyl)aminonitriles to the corresponding amides and acids.

3. It has been shown that the interaction of the obtained di(2-chloroethyl)amino compounds with aniline leads mainly to the formation of derivatives of 1,4-diphenylpiperazine.

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STUDY OF THE MECHANISM OF ISOMERIZATION OF NAPHTHALENEMONOSULFONIC ACIDS BY THE TAGGED-ATOM METHOD

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In spite of the fact that the isomeric conversions of aromatic sulfonic acids were discovered in the 1870's [1] and have been studied repeatedly since then, there still remains much doubt as to the mechanism of these processes. The isomerization of naphthalenemonosulfonic acids is an example. The first investigators [2] who discovered the conversion of 1-naphthalenesulfonic acid to the 2-isomer on heating it in sulfuric acid to 160-170° propounded the hypothesis that the reaction proceeds by means of a hydrolytic splitting of the 1-sulfonic acid to naphthalene, with subsequent resulfonation of the latter in a β-position. Since the 2-sulfonic acid also is capable of being hydrolyzed [2, 3] (see also [1]), the isomerization process should be reversible. This was established experimentally by Euwes [4], who arrived at the equilibrium positions at 143 and 158°, starting both from the 1- and also from the 2-isomer. In agreement with the intermolecular hydrolytic mechanism of isomerization, the 2-sulfonic acid, which is more stable with respect to hydrolysis, predominates in the equilibrium mixture.

A number of facts, however, in the opinion of Euwes, did not fall within the bounds of the assumed mechanism, and he assumed for their explanation the possibility that under certain conditions (at 130° or below in concentrated sulfuric acid) there takes place an irreversible intramolecular conversion of the 1-naphthalenesulfonic acid to the 2-isomer. This hypothesis was later subjected to criticism [1, 5, 6] which, however, was not acknowledged by all to be convincing [7, 8].

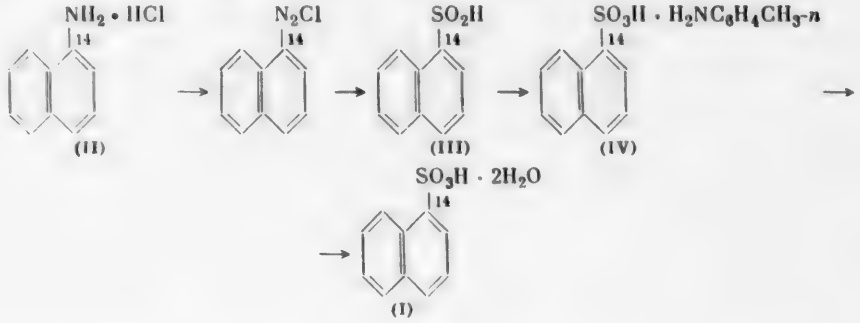
In recent years, a number of studies have been conducted using tagged sulfur S^{35}, in which it was attempted to determine the mechanism of isomerization of the naphthalenemonosulfonic acids, based on the extent of interchange of the HO_3S group between the sulfonic acid and the sulfuric acid in the process of isomerization [9-11]. Thereby it was found that at 140-160° in 75-78% sulfuric acid* the isomerization of the 1-sulfonic acid to the 2-isomer is accompanied by practically complete interchange [9, 11], which is in agreement with the intermolecular hydrolytic mechanism of the process. However, in more concentrated sulfuric acid (91-94%) at 150-160° the isomerization takes place to a considerable extent (20-50%) without interchange of the HO_3S group with the medium [9, 10]. The absence of complete interchange with the medium was also noted in the case of isomeric conversions of o- and p-toluenesulfonic acids [12, 13]. In the opinion of Shilov and Vainshtein [10, 12], the incomplete interchange on conducting the process in concentrated sulfuric acid is explained either by a partial occurrence of the isomerization through an intramolecular mechanism or by resulfonation of the naphthalene molecule by the HO_3S^+ ion formed on hydrolytic splitting, having insufficient time to mix with the particles of the medium ("cage" effect).

In order to evaluate the reality of these hypotheses and primarily that of the role of intramolecular mechanism, we decided to study the isomerization of 1-naphthalenesulfonic acid tagged with radiocarbon in position 1. In this case, with the process occurring by an intramolecular mechanism, the isomerization should result in the formation of the 2-isomer also tagged in position 1 (compare [14, 15]); with the conversion occurring by an intramolecular

* In all cases the sulfuric acid concentration is given with allowance having been made for the water introduced with the crystalline hydrate of the sulfonic acid.

mechanism with the intermediate formation of naphthalene, there should be obtained an equimolar mixture of 2-naphthalenesulfonic acids tagged in positions 1, 4, 5, and 8, in view of the equal probability of sulfonating the naphthalene in any β-position.

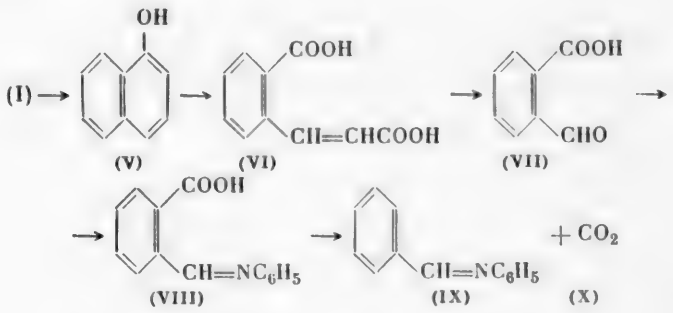
We synthesized the 1-naphthalenesulfonic acid-1-C^{14} (I) need for conducting this investigation from 1-naphthylamine-1-C^{14} hydrochloride [14] (II) according to the following scheme:



Replacement of the amino group by the HO_2S group was accomplished by the Gatterman method [16] by treatment of the diazo compound with sulfur dioxide in the presence of metallic copper. The yield of the 1-naphthalenesulfinic acid-1-C^{14} (III) was 78.5%. In working out this stage on untagged compounds, it was found that in individual experiments the yield of sulfinic acid fell as low as approximately 5%. We succeeded in determining that this was related to destruction of the sulfinic acid occurring in the copper sludge, in the process of autoxidation of the latter (compare [17]) in contact with air while processing the reaction mass. It is interesting to compare this observation with the data of [18] on the ready oxidizability of copper salts of sulfinic acids by atmospheric oxygen.

The oxidation of 1-naphthalenesulfinic acid-1-C^{14} to 1-naphthalsulfonic acid-1-C^{14} was achieved by the action of hydrogen peroxide in alkaline solution, from which the sulfonic acid that was formed was recovered in the form of the difficultly water-soluble p-toluidine salt (IV). On passing an alcoholic solution of this salt through SDV-3 cation exchange resin, the 1-naphthalenesulfonic acid-1-C^{14} was obtained in the free state in the form of the dihydrate. The total yield based on the 1-naphthylamine-1-C^{14} hydrochloride was 62%.

For proving the position of the "tag" in the 1-naphthalenesulfonic acid thus synthesized, the compound was split, making it possible to determine the radioactivity of the carbon atom in position 1 in comparison with the total radioactivity of the molecule.



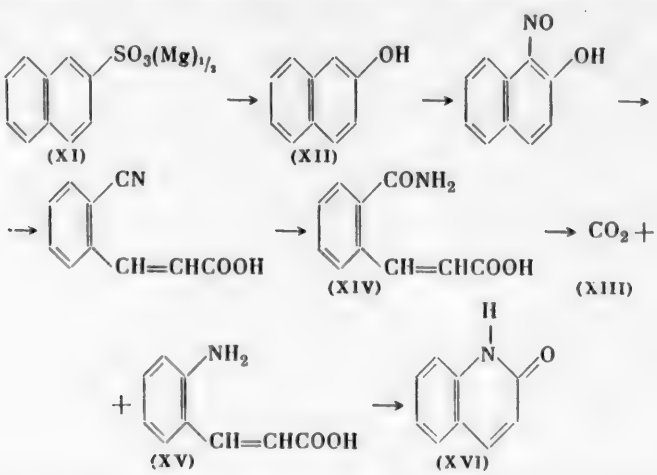
For this, the sulfonic acid was subjected to alkaline fusion, and the resulting 1-naphthol (V) (obtained with 77% yield) was oxidized further with peracetic acid [19] to o-carboxycinnamic acid (VI) with a 41% yield. The latter was oxidized by the action of potassium permanganate in alkaline medium [20] to o-carboxybenzaldehyde (VII), recovered in the form of the Schiff base (VIII) with 47% yield. Decarboxylation of this base was accomplished successfuly by heating at 320° in the presence of copper bronze.*

* Based on the method described for the anil of opianic acid [21].

Compound	Radioactivity	
	μC/mole	%
o-$C_6H_4(CONH_2)CH = CHCOOH$	2941	100
CO_2	703.5	24
o-$C_6H_4(NH_2)CH = CHCOOH$	2179	74
o-C_6H_4(NH)CH = CHCO	2174	

Measurement of the radioactivity of the products of the decarboxylation – benzylideneaniline (IX) and carbon dioxide (X) – showed that practically all of the radioactivity of the o-carboxybenzylideneaniline (VIII) passes into the carbon dioxide. This indicates that the tagged 1-naphthalenesulfonic acid which we synthesized contains radiocarbon only in position 1.

Isomerization of the dihydrate of 1-naphthalenesulfonic acid-1-C^{14} was carried out by heating it with 3.7 moles of 100% sulfuric acid (taking into account the hydrate water of the sulfonic acid, the sulfuric acid concentration in the mixture was 91%) for 30 minutes at 160°. The 2-naphthalenesulfonic acid-x-C^{14} which was formed was recovered from the reaction mass in the form of the magnesium salt (XI) according to the method of [22] and further converted by heating with 30% sodium hydroxide solution at 350-360° [23, 24] to 2-naphthol-x-C^{14} (XII) with 82% yield based on the magnesium salt of the 2-sulfonic acid. For determining the position of the "tag," the naphthol was split by a scheme that we had developed previously [14], permitting removal of the carbon atom occurring in position 1 in the form of carbon dioxide.



The ratio of the molar radioactivities of the carbon dioxide (XIII) and the trans-o-carbamidocinnamic acid-x-C^{14} (XIV) thereby should be equal to 1 : 1 in case the isomerization takes place according to an intramolecular mechanism and there is no migration of the sulfo group from position 2 to position 3, and a 0.25 : 1 ratio in case the isomerization takes place according to an intermolecular hydrolytic mechanism, because in the first case there would be formed only 2-naphthalenesulfonic acid-1-C^{14}, but in the second, an equimolecular mixture of the 2-isomers, tagged in positions 1, 4, 5, and 8. The results of radioactivity measurement of the trans-o-carbamidocinnamic acid-x-C^{14} (XIV), trans-o-aminocinnamic acid-x-C^{14} (XV), carbostyryl-x-C^{14} (XVI), and carbon dioxide (XIII) are presented in the table.

The results obtained demonstrate that in the isomerization of 1-naphthalenesulfonic acid-1-C^{14} there is formed an equimolar mixture of 2-naphthalenesulfonic acids tagged in positions 1, 4, 5, and 8, i.e., that the migrating sulfo groups enter into any of the 4 β-positions with equal probability. This indicates that under the conditions we selected the intramolecular mechanism does not play a substantial role, even though in studies utilizing tagged sulfur it had been established that isomerization under similar conditions takes place to the extent of 30% [10] (or even more [9]) without exchange of the sulfo group with the medium. The combination of these facts may be explained if one adopts the hypothesis of Shilov and Vainshtein [10, 12] on the manifestation in the given case of a "cage" effect. According to this hypothesis, the particles formed on hydrolysis of the α-naphthalenesulfonic acid (the naphthalene molecule and the detached sulfo group) exist in a "cage" of solvent molecules [25], which holds them for a certain time, not allowing diffusion into the solution; this retention increases the probability of sulfonation of the naphthalene molecule by exactly that sulfonating particle that was split out on hydrolysis. However, it should be kept in mind that the "cage" effect up to now has been observed only for the case of the formation of very reactive pairs of the type radical – radical (for example, see [26, 27]), where almost every collision of the particles of the pair leads to

reaction between them. In the case of formation of a pair of the neutral molecule – ion type or a pair of two neutral molecules, where by no means every collision of the pair partners leads to reaction, the manifestation of a "cage" effect has a low probability [26, 28, 29]. Moreover, the possibility of interaction of the participants of the pair with the solvent, for example:

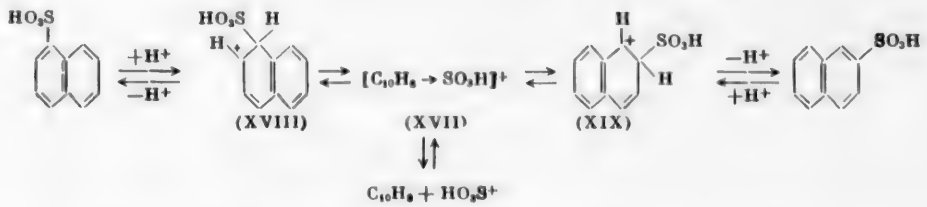
$$HO_3\overset{\bullet}{S}^+ + H_2SO_4 \longrightarrow H_2\overset{\bullet}{S}O_4 + HO_3S^+; \quad \overset{\bullet}{S}O_3 + H_2SO_4 \longrightarrow H_2\overset{\bullet}{S}O_4 + SO_3$$

and the high temperature of the system in carrying out the isomerization of naphthalenemonosulfonic acids still further reduce such probability (compare [30, 31]).

In our view it is a more real hypothesis that the detached sulfo group is held close to the naphthalene molecule on account of interaction with the cloud of π-electrons of this molecule, i.e., that on hydrolysis of the sulfonic acid there is formed an intermediate compound of the π-complex type postulated by Dewar [32]. According to modern concepts [33], there exists a definite, even though small, energy barrier hindering the decomposition of such complexes into the components.

The presence of this barrier increases substantially the possibility of sulfonation of the naphthalene molecule by exactly the same sulfo particle that was detached on hydrolysis. This also explains the incomplete exchange of the sulfonic acid HO_3S group with the medium in experiments with tagged sulfur. The equal probability of entry of the sulfo group into any of the four β-positions, which was established in our work, can be caused either by the migrating group being located in an intermediate complex that is symmetrical relative to the four β-positions (compare [13]), or by its being able to shift freely in this complex along the border of the π-electron cloud of the aromatic molecule (compare [32]).

It is easy to see that in such an interpretation of the presently available data there is no necessity for the assumption of two different mechanisms of isomerization of the aromatic sulfonic acids (compare [10, 13]) – intramolecular (without exchange of the sulfo group with the medium) and intermolecular. In particular, the mechanism of interconversions of naphthalenemonosulfonic acids can be represented by the following general scheme:*



According to this scheme, the extent of interchange of the sulfonic acids' HO_3S group with the medium during isomerization is determined by the ratio of the rates of conversion of the intermediate complex (XVII) to σ-complexes (XVIII and XIX) and its decomposition into the components.** The rate of the latter process should increase with an increase in the solution concentration of particles capable of bonding with the detached sulfo group, for example, water molecules. This makes it possible to understand why complete interchange of the HO_3S groups between the monosulfonic acid and the medium is observed on conducting the isomerization of naphthalenemonosulfonic acids in dilute (75-78%) sulfuric acid [9, 11].

It should be emphasized that the mechanism we are proposing is still only a working hypothesis, intended to explain the presently available experimental facts. To ascertain the reality of this hypothesis, we contemplate con-

* There is basis for assuming [34] that in the hydrolysis of sulfonic acids the $ArSO_3^-$ ion, and not the neutral $ArSO_3H$ molecule, is subjected to attack by the proton. In this case the SO_3 molecule rather than the HO_3S^+ ion would enter into the intermediate complex; the former can also play the role of an electron acceptor; compare the formation of adducts of SO_3 with amines [35].

** It is not excluded that the exchange in the intermediate complex (XVII) can proceed not only on account of its decomposition, but also by means of replacement of the HO_3S group by an analogous group from the surrounding H_2SO_4 molecules.

ducting an analogous investigation using a double tag (C^{14} and S^{35}), in order to determine in a single experiment the extent of interchange of the sulfo group with the medium and its distribution among the individual β-position in the isomerization product.

EXPERIMENTAL

1-Naphthalenesulfinic acid-1-C^{14}. A 100 ml three-necked flask fitted with stirrer, reflux condenser, and thermometer was charged with 2.65 g of 1-naphthylamine-1-C^{14} [14] (radioactivity ~ 80 mC/mole), 2.11 g nonradioactive 1-naphthylamine, 4.6 ml concentrated hydrochloric acid, and 61 ml water. The mixture was heated with stirring to 95-98° to dissolve the hydrochloride and then cooled rapidly in a snow-salt mixture, at the same time adding 11.6 ml of concentrated hydrochloric acid. To the resulting slightly pinkish slurry of the 1-naphthalenesulfonic acid-1-C^{14}, 6.8 ml of 4.0 N sodium nitrite solution was added at –2°, beneath the surface of the slurry. Stirring at this moment must be especially vigorous. After disappearance of nitrous acid from the reaction mass (iodine – starch paper test), diazotization was continued at 0-2°, adding nitrite solution dropwise until excess nitrous acid was retained for 15 min. The excess nitrous acid was decomposed by adding 0.1 g urea, and the brown solution of the diazo compound was filtered through a layer of absorbent cotton.

Preparation of the metallic copper [17] was carried out in parallel with the diazotization of the 1-naphthylamine-1-C^{14} hydrochloride. A 42 g quantity of moist copper paste and 200 ml of saturated aqueous sulfur dioxide solution* were charged to a 500 ml four-necked flask fitted with a stirrer, dropping funnel, and tube extending to the bottom for introduction of sulfur dioxide gas. Having started the sulfur dioxide stream into the flask (100-150 ml/min), to the copper suspension at room temperature with vigorous stirring there was added over 30 min (not more rapidly!) the cold solution of the diazo compound (at the moment of falling of a drop into the suspension, the formation of a yellow complex was observed). Stirring and passage of sulfur dioxide were continued for 1.5 hr longer.

On the following day the brown precipitate was filtered off (filtrate I), and the sulfinic acid was washed out of it with 225 ml of ether. (The sediment on the filter contains the main part of the sulfinic acid formed in the reaction, but if during the filtration it is pressed and left for some time in air, a strong evolution of heat is observed, and the sulfinic acid content in the sediment decreases to zero. The heat evolution from the sediment is related to processes of oxidation by atmospheric oxygen in which, apparently, the sulfinic acid also takes part [18]. Therefore, it is necessary to watch that the sediment is covered with a liquid layer at all times during the filtration and washing with ether.)

The olive-colored ether solution was washed with a 5% sodium carbonate solution (five times with 15-ml portions; the aqueous layer in the last three washes should have an alkaline reaction), and the sodium carbonate solution (chilled to 0°) was acidified with concentrated hydrochloric acid, recovering the 1-naphthalenesulfinic acid-1-C^{14} separated in the form of an oil which, however, crystallized rapidly to a yellowish-gray mass. The suspension was held 1 hr on ice; then the sulfinic acid was filtered off, washed with cold water, and left to dry in a desiccator over calcium chloride. Yield of acid 4.14 g, m.p. 82-82.3°.

From the filtrate I by extraction with ether and then extraction of the ether solution which sodium carbonate, there was recovered 0.18 g of the sulfinic acid with m.p. 84-85°. Total yield 4.32 g (78%).

In the literature [36] melting points from 84 to 104° are cited for 1-naphthalenesulfinic acid.

1-Naphthalenosulfonie acid-1-C^{14}. To a 50 ml three-necked flask fitted with a thermometer, reflux condenser, and a stirrer passing through the latter, there were charged 4.43 g of 1-naphthalenesulfinic acid-1-C^{14} and a solution of 0.92 g sodium hydroxide in 22.5 ml water. To the resulting light-brown solution, at room temperature with vigorous mixing, there was added in one dose 3.62 g of 27% aqueous hydrogen peroxide solution. The solution temperature thereby increased to 70-75°. Stirring was continued for 1 hr more,** after which the solution was filtered from the sediment, heated to 90°, and treated with a hot solution of 2.94 g p-toluidine and 3.4 ml of concentrated hydrochloric acid in 4.5 ml of water. The p-toluidine salt of the sulfonic acid was precipitated upon chilling the resulting violet-colored solution in snow. The thick slurry was held 1 hr at 0°, and the salt was filtered

* Saturation was conducted at 0°, up to a weight increase of 17-20 g per 100 ml water.

** Completion of the reaction was checked by taking one drop of the reaction mixture, acidifying with hydrochloric acid, and adding an aqueous ferric chloride solution; with the presence of sulfinic acid, a precipitate of the insoluble orange iron salt should be formed [37].

off, pressed thoroughly, and dried to constant weight in a desiccator over calcium chloride (4 days without vacuum and 2 days in vacuum). Yield of brownish-gray product 7.61 g, m.p. 166-168°. It should be noted that the melting point of the p-toluidine salt depends strongly on the degree of its dehydration. On drying samples (obtained in model experiments) to constant weight in vacuum at 65°, the melting point increased from 166 to 189-190°. M.p. 181° is cited in the literature [38] for the p-toluidine salt of 1-naphthalenesulfonic acid.

The 1-naphthalenesulfonic acid-1-C^{14} was recovered in the free form by the use of cation exchange resin SDV-3 (capacity 4 meq/g). A 7 g quantity of the resin was covered with 50 ml of water and allowed to stand 12-15 hr. The swollen resin was transferred to a column (diameter 10 mm, height 300 mm) and washed first with 300 ml of 0.1 N hydrochloric acid, then with water until chloride ion was eliminated, and finally with 75 ml of alcohol. A 3.8 g quantity of the p-toluidine salt was dissolved in 40 ml of alcohol, and the brownish-red solution was filtered through the column of ion exchange resin. The filtration rate was 4-5 drops per minute. The column was washed with 110 ml of alcohol, the filtrates were combined, and the alcohol was distilled off under vacuum, with a bath temperature not greater than 50°. The brown oil remaining in the flask was cooled to 0°, and 6.2 ml of concentrated hydrochloric acid was added. The 1-naphthalenesulfonic acid-1-C^{14} that precipitated was filtered off, washed with 7 ml of concentrated hydrochloric acid, and dried first over a 50% sodium hydroxide solution (4 days), then over solid potassium hydroxide (to constant weight), and finally in air* (2 days). The total yield of slightly grayish dihydrate of 1-naphthalenesulfonic acid-1-C^{14} was 2.32 g (78.8%), m.p. 88.0-88.5°. According to the data of [39], the dihydrate melts at 87-88, 90°.

The 1-naphthalenesulfonic acid-1-C^{14} was also identified on the basis of the ultraviolet absorption spectrum, taken for an alcoholic solution in the SF-4 apparatus. The position of the absorption maxima at 224, 274.5, 283 (inflection point), 313, and 317 mμ agreed with those cited in the literature [40].**

Splitting of 1-Naphthalenesulfonic Acid-1-C^{14}

1-Naphthol-1-C^{14} (V). A 26 ml sealed stainless steel tube was charged with 1.20 g of 1-naphthalenesulfonic acid-1-C^{14}, 2.76 g sodium hydroxide, and 6.3 ml water. The tube was immersed in a Woods metal bath preheated to such a temperature that on immersion of the tube the temperature fell to 350°. After 30 min at 350-355° the tube was withdrawn from the bath and cooled rapidly with cold water. The contents of the tube were digested with hot water; the alkaline solution was treated with carbon, filtered, and acidified with concentrated hydrochloric acid to recover the 1-naphthol-1-C^{14}. Yield 0.55 g (77%), m.p. 91.7-92.5°. According to literature data, m.p. from 94 to 96° [42].

o-Carboxy-C^{14}-cinnamic acid (VI). To a mixture of 0.268 g of 1-naphthol-1-C^{14} and 0.320 g untagged 1-naphthol, there was added in a single dose 8 ml of a solution of 0.94 g peracetic acid in acetic acid. An exothermal reaction began after several minutes. The flask was immersed periodically in cold water, holding the temperature of the reaction mixture between 34 and 45°. After the self-heating ceased (in 30 min), the red solution was allowed to stand 5 days, shaking from time to time. The colorless precipitate that formed during this time was filtered off, washed with acetic acid, and held 2 days under vacuum over a concentrated sodium hydroxide solution. Yield of o-carboxy-C^{14}-cinnamic acid 0.316 g (41%), m.p. 170.5-172.5°.

In the literature [43] for o-carboxycinnamic acid contradictory data are cited for melting point, from 173 to 205°.

o-Carboxy-C^{14}-benzaldehyde (VII) and o-carboxy-C^{14}-benzylideneaniline (VIII). A three-necked flask fitted with stirrer and dropping funnel was charged with 0.316 g of o-carboxy-C^{14}-cinnamic acid and a solution of 0.317 g sodium hydroxide in 20 ml water. A total of 29 ml of 2% potassium permanganate solution was added dropwise over ~1 hr to the alkaline solution, with vigorous stirring at room temperature. The resulting suspension was allowed to stand for 30 min and then filtered, and the precipitate was washed with a small quantity of water. The slightly pinkish filtrate was decolorized by treatment with carbon, acidified with concentrated hydrochloric acid to acid reaction (Congo), and extracted with ether for 35 hr in a continuous extractor (volume of aqueous layer ~50 ml). The ether extract after distilling off the ether gave 0.210 g of o-carboxy-C^{14}-benzaldehyde (VII) with m.p. 78-85°.

* The air-dried 1-naphthalenesulfonic acid contains 2 molecules of water of crystallization [39].

** In this work a single maximum was recorded at 315 mμ; however, according to [41], there are two absorption maxima in this region at 312.5 and 317 mμ.

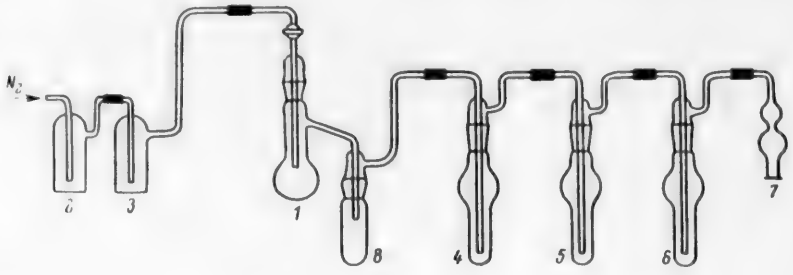
To obtain the Schiff base, the aldehyde was dissolved in 1.3 ml of 1 N sodium hydroxide solution and 0.5 ml alcohol, heated to 70°, and treated by stirring with 0.85 ml of an alcoholic solution of aniline containing 0.13 g of the latter. The liquid became turbid, and a colorless sediment was precipitated. The suspension was held 20 min more at 70°; then it was cooled to 5°, and 0.60 ml of 10% hydrochloric acid was added. After ~0.5 hr the colorless precipitate was filtered off, washed with water and 3 ml aqueous alcohol (1 : 2), and dried in vacuum over calcium chloride. Yield 0.174 g (47% based on 1-carboxy-C^{14}-cinnamic acid), m.p. 173-174°. According to the data of [44], o-carboxybenzylideneaniline has m.p. 174°.

Found %:* C 74.6, 74.6. $C_{14}H_{11}O_2N$. Calculated %: C 74.7.

Radioactivity: 3180 μC/mole.

Decarboxylation of o-Carboxy-C^{14}-benzylideneaniline

The decarboxylation was carried out in the apparatus depicted in the figure. The flask 1 was charged with 0.254 g of o-carboxy-C^{14}-benzylideneaniline and 0.026 g of copper bronze, after which air was removed from the



apparatus by purging with nitrogen washed with sodium hydroxide solution and concentrated sulfuric acid (wash bottles 2 and 3). Continuing the nitrogen purge, the traps 4, 5, and 6 protected by the Ascarite tube 7, were each filled with 10 ml of 0.255 N barium hydroxide solution containing 20 g/liter of barium chloride, and the flask 1 was immersed in a bath heated to 320°.** The reaction mixture was held 1 hr at this temperature (nitrogen feed rate ~7 ml/min). The evolved carbon dioxide was absorbed in the traps 4-6, and the benzylideneaniline was distilled into the collector 8. After completion of the holding period, the nitrogen purge was continued for 1 hr longer at ~20° for complete displacement of the carbon dioxide from the reaction flask. Then the excess barium hydroxide in the traps 4-6 was backtitrated with 0.1 N hydrochloric acid. The consumption of the latter was 56.48 ml, which corresponds to absorption of 88.1% of the carbon dioxide. The radioactivity of the barium carbonate obtained was equal to 3260 μC/mole.

Yield of benzylideneaniline 0.162 g (79%), m.p. 48-50°. On recrystallization from aqueous alcohol (1 : 1.5), obtained 0.115 g of lustrous crystals with m.p. 50.5-51.5°. According to the data of [45], benzylideneaniline has m.p. 54°.

Found %: C 85.0, 84.8.*** $C_{13}H_{11}N$. Calculated %: C 86.2.

Radioactivity: 41.5, 43.6 μC/mole.

Isomerization of 1-naphthalenesulfonic acid-1-C^{14}. A mixture of 1.394 g of the dihydrate of 1-naphthalenesulfonic acid-1-C^{14}, 2.802 g of untagged dihydrate of 1-naphthalenesulfonic acid (obtained analogously from 1-naphthylamine), and 6.26 g of 100% sulfuric acid was sealed in a glass ampule, which was placed in a steel tube.

* The completeness of combustion was checked by the Van Slyke method. For the method of determining radioactivity, see [14]. The analysis is for a mixture of 0.174 g of the material obtained and 0.870 g of untagged compound.

** The decarboxylation also takes place at a lower temperature (250°). The use of a temperature above 300° is explained by the advisability of distilling off the benzylideneaniline from the sphere of reaction.

*** The incompleteness of combustion in this case is evidently explained by the fact that the benzaldehyde evolved on decomposition of benzylideneaniline in acidic medium is partially vaporized, not having enough time to be oxidized.

The tube was filled with water to improve heat transfer. The hermetically sealed tube was immersed in a Woods metal bath preheated to such a temperature that after immersing the tube the final temperature was 160°. After heating 30 min at 160-161°, the tube was withdrawn from the bath and cooled rapidly with cold water. The contents of the ampule after opening were diluted with 30 ml water, treated with carbon, and filtered. The dark-colored filtrate was heated to 98°, 6.8 ml of a 15% magnesium sulfate solution was added, and the mixture was cooled slowly so that in 3 hr the temperature had dropped to 35°. The slow cooling favors precipitation of a more pure magnesium salt of the 2-isomer [22]. On the following day the crystallized hexahydrate of the magnesium salt of 2-naphthalenesulfonic acid-x-C^{14} was filtered off and washed with 10 ml water. For dehydration, this salt was dried first in a desiccator over calcium chloride, and then 13 hr at 110° (see [46]). Yield of anhydrous salt 1.16 g (30.8% based on the 1-naphthalenesulfonic acid-1-C^{14} taken for isomerization).

Splitting of 2-Naphthalenesulfonic Acid-x-C^{14}

2-Naphthol-x-C^{14}. Alkaline fusion of the magnesium salt of 2-naphthalenesulfonic acid-x-C^{14} was accomplished by heating it (1.16 g) with 12 ml of a 30% sodium hydroxide solution under the same conditions as those used in the fusion of 1-naphthalenesulfonic acid-x-C^{14}.

The resulting reaction mass was diluted with 30 ml of water, treated with carbon, and filtered. On acidification of the filtrate with concentrated hydrochloric acid, a colorless precipitate of 2-naphthol-x-C^{14} was formed. It was established in model experiments that the 2-naphthol thus obtained is very difficult to filter out. To facilitate the filtration, the suspension of 2-naphthol-x-C^{14} was heated on a steam bath until the precipitate was almost completely dissolved and then allowed to cool slowly. On the following day the 2-naphthol-x-C^{14} was filtered off and washed with water. Yield of 2-naphthol-x-C^{14} 0.58 g (77%), m.p. 118.0-119.5°.

According to literature data [47], m.p. 122-123°.

From the filtrate, by extraction with ether with subsequent reprecipitation from alkali, there was recovered an additional 0.04 g (5.3%) of a more contaminated product (m.p. 96-100°), which was not investigated further.

1-Nitroso-2-naphthol-x-C^{14}, cis-o-cyanocinnamic acid-x-C^{14}, and trans-o-carbamidocinnamic acid-x-C^{14}. The obtained 2-naphthol-x-C^{14} was converted further by methods we described previously [14, 15], through 1-nitroso-2-naphthol-x-C^{14} (yield 92%) to cis-o-cyanocinnamic acid-x-C^{14} (yield 62.2%) with m.p. 134.5-136.0°. In the literature [48] m.p. 137° is cited for cis-o-cyanocinnamic acid.

On acid hydrolysis of cis-o-cyanocinnamic acid-x-C^{14} (see [14] for method), a 53.2% yield was obtained of trans-o-carbamidocinnamic acid-x-C^{14} with m.p. 231.0-233.0°. According to the data of [49], the melting point of trans-o-carbamidocinnamic acid is 239°. The acid obtained (XIV) (0.2345 g) and 0.586 g of untagged trans-o-carbamidocinnamic acid (m.p. 237-238°) were reprecipitated from 5% sodium carbonate solution, obtaining 0.747 g of acid with m.p. 236-237°.

Found %: C 62.2. $C_{10}H_9O_3N$. Calculated %: C 62.8.

Radioactivity: 2925 μC/mole.

Analysis of a sample purified further by recrystallization from alcohol gave the following results.

Found %: C 62.8. $C_{10}H_9O_3N$. Calculated %: C 62.8.

Radioactivity: 2957 μC/mole.

trans-o-Aminocinnamic acid-x-C^{14} (XV). We had described previously [14]* the method of splitting the trans-o-carbamidocinnamic acid-x-C^{14} into trans-o-aminocinnamic acid-x-C^{14} and carbon dioxide based on the Hoffman reaction. A 200 mg quantity of the acid was taken for splitting. The yield of carbon dioxide was 100.5%, and its molar radioactivity (in the form of barium carbonate) 703.5 μC/mole.

From the acidic solution after displacement of the carbon dioxide, there was recovered (by treatment with 5% sodium hydroxide solution to almost neutral reaction to litmus) 0.0975 g (57%) of the lemon-yellow trans-o-aminocinnamic acid-x-C^{14} with m.p. 148-149.5°. From the filtrate by extraction with ether and passing hydrogen chloride

* In the method cited, directions were omitted on the necessity for holding the reaction mass after adding the hypobromite solution (in addition to 10 min at 0°) another 30 min at room temperature, and only then to begin the heating. Increasing the period of holding at low temperature eliminates side processes of bromination.

into the ether extract, subsequently dissolving the resulting hydrochloride in a small quantity of water and adding an equimolar quantity of sodium hydroxide, there was recovered an additional 0.034 g (20%) of trans-o-aminocinnamic acid-x-C^{14} with m.p. 153-154°. In the literature [49] for trans-o-aminocinnamic acid, m.p. 158° is cited. Analysis of the latter sample gave the following results.

Found %: C 66.0. $C_9H_9O_2N$. Calculated %: C 66.2.

Radioactivity 2179 μC/mole.

Carbostyryl-x-C^{14} (XVI). A 0.0976 g quantity of trans-o-aminocinnamic acid-x-C^{14} was heated in a flask with a reflux condenser with 0.12 ml of concentrated hydrochloric acid and 9 ml of water, and the resulting solution was boiled 14 hr. The colorless precipitate that formed on cooling was filtered off (the suspension having been neutralized previously by the addition of sodium carbonate solution) and dissolved in 7 ml of a 7% sodium hydroxide solution. On passing carbon dioxide through the filtered alkaline solution, the colorless carbostyryl-x-C^{14} was precipitated, yield 48 mg (55%). After purifying by recrystallization from water and drying 3 hr over calcium chloride in vacuum at 100°, the preparation melted at 190-192°. According to literature data [50], m.p. 196°.

Found %: C 74.5. C_9H_7ON. Calculated %: C 74.4.

Radioactivity: 2174 μC/mole.

SUMMARY

1. Starting from 1-naphthylamine-1-C^{14}, 1-naphthalenesulfonic acid-1-C^{14} has been synthesized with 62% yield; the position of the "tag" in the latter has been confirmed by splitting according to a scheme permitting the removal in the form of CO_2 of the carbon atom from position 1 of the naphthalene nucleus.

2. It has been established that during isomerization of 1-naphthalenesulfonic acid-1-C^{14} to the 2-isomer at 160° in 91% sulfuric acid the sulfo group migrates with equal probability to any of the four β-positions.

3. A possible mechanism of the isomerization of naphthalenemonosulfonic acid is discussed.

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STERIC HINDRANCE AND REACTIVITY OF ORGANIC COMPOUNDS

II. β-NAPHTHALENESULFONIC ACID AS A CATALYST FOR ISOMERIZATION OF COMPOUNDS WITH STERICHINDRANCE*

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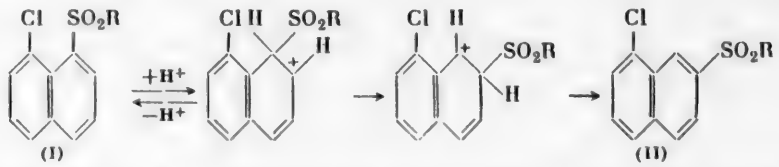
We established previously [1] that alkyl 1-chloronaphthyl-8 sulfones (I) in which steric hindrance prevents the chlorine and the sulfur atoms from lying in the plane of the naphthalene nucleus, are isomerized by heating with concentrated hydrochloric acid at 200-220° into alkyl 1-chloronaphthyl-7 sulfones (II).

According to contemporary ideas [2] on the mechanism of migration of substituents in aromatic compounds, this conversion is the result of an attack of the proton on the carbon atom attached to the sulfonyl group.



The conditions for this attack are unfavorable in an aqueous solution of an acid as the sulfone has to compete for the proton with much more basic water molecules. In view of the fact that the rate of the reactions catalyzed by proton donors are directly related to the acidity function (H_0) of the medium (log $k = -H_0$ + const; see [3]), it was to be expected that the above conversion would be achieved at a much lower temperature in a medium with a high value of $-H_0$, i.e., a high tendency to donate a proton to a neutral base. This condition is satisfied by sulfuric acid, in particular, as for 100% sulfuric acid at 25°, $H_0 = -11.1$, while for concentrated hydrochloric acid, $H_0 = -4.0$ [4]. However, the use of sulfuric acid as the medium is complicated by the possibility of sulfonation (cf. conditions for sulfonation of 1,8-dichloro- and 1,8-chloronitronaphthalenes [5]). This drawback is eliminated to a considerable extent by the use of aromatic sulfonic acids, which are similar to sulfonic acid in proton-donating power [6].

In actual fact, the use of anhydrous β-naphthalenesulfonic acid instead of hydrochloric acid made it possible to reduce the temperature of isomerization of alkyl 1-chloronaphthyl-8 sulfones considerably. Thus, in the presence of this acid, methyl 1-chloronaphthyl-8 sulfone (I, R = CH_3) was converted comparatively readily into methyl 1-chloronaphthyl-7 sulfone (II, R = CH_3) even at 110°. The isomerization temperature could not be reduced further because of the high melting point of anhydrous β-naphthelenesulfonic acid (m.p. 103.5-104° [7]).

As was to be expected, the isomerization of methyl 1-chloronaphthyl-8 sulfone was retarded by the addition of water to the reaction mixture. The substance was not isomerized when heated at 110° with β-naphthalenesulfonic acid trihydrate or with a 30% aqueous solution of the acid and the starting sulfone could be recovered in 90-95% yield. The retarding effect of water was caused by the fact that, being a strong base, it reduces the capacity of the medium to donate a proton to such a weak base as the molecule of an aromatic compound. This may be illustrated by the fact that with a change from 100% to 65% sulfuric acid (3 moles of water per mole of sulfuric acid), the acidity function changes from −11.1 to −5.0 [4].

It should be noted that the acidity of anhydrous β-naphthalenesulfonic acid was still inadequate to produce isomerization of compounds without steric hindrance (the reasons for more ready isomerization of compounds with

* See [1] for Communication I.

steric hindrance between the substituents are discussed in [1]). Thus, methyl naphthyl-1 sulfone did not change when heated with this acid, while it was converted into the 2-isomer in the presence of zinc chloride in a stream of hydrogen chloride at 200° [8].

The results obtained thus confirm the hypothesis on the role of a proton in the process examined and make it possible to plan searches for more efficient isomerization catalysts.

EXPERIMENTAL

The synthesis of the sulfones used in this work was described previously [1]. β-Naphthalenesulfonic acid trihydrate was prepared by the procedure in [9] and had m.p. 82.5-83° (literature data [7]: m.p. 83°). β-Naphthalenesulfonic acid monohydrate was obtained by dehydration of the trihydrate in vacuum over calcium chloride and had m.p. 124-125° (literature data: m.p. 125.5°).

Isomerization. Experiment 1. A 2.37 g sample of β-naphthalenesulfonic acid monohydrate was dehydrated by heating at 110° for 8.5 hr in a stream of dry air. The loss in weight corresponded to the complete removal of the water of hydration. To the anhydrous acid was added 0.50 g of methyl 1-chloronaphthyl-8 sulfone (m.p. 124.5-126°) and the mixture, which was protected from atmospheric moisture with a tube of magnesium chlorate, heated for 20 hr at a bath temperature of 110°. The mixture was then treated with hot water and the insoluble residue collected, washed with 10% alkali solution, and dried; it weighed 0.49 g and had m.p. 147-152°. Recrystallization from alcohol raised the melting point of the product obtained to that of methyl 1-chloronaphthyl-7 sulfone (m.p. 160.5-161.0° [1]) and a mixed melting point was not depressed. Their ultraviolet absorption spectra were also found to be identical (see [10] for the spectra).

Experiment 2. A mixture of 0.50 g of methyl 1-chloronaphthyl-8 sulfone and 2.8 g of β-naphthalenesulfonic acid trihydrate was heated in a sealed glass tube at 110° for 15 hr. From the reaction mixture we isolated 0.45 g of the starting sulfone with m.p. 124-126°.

An analogous result was obtained by heating 1.00 g of the sulfone with 5.50 g of the trihydrate in 9.0 ml of water.

Experiment 3. A mixture of 0.47 g of methyl naphthyl-1 sulfone (m.p. 100.5-101.5°) and 2.87 g of β-naphthalenesulfonic acid monohydrate was heated at 110° for 8.5 hr in a stream of air to dehydrate the sulfonic acid and then for a further 13 hr. From the reaction mixture we isolated 0.42 g of the starting substance with m.p. 99-100.5°.

SUMMARY

Methyl 1-chloronaphthyl-8 sulfone is isomerized smoothly into methyl 1-chloronaphthyl-7 sulfone by heating with anhydrous β-naphthalenesulfonic acid at 110°. The introduction of water into the reaction mixture retards isomerization.

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STEREOCHEMICAL INVESTIGATIONS

VII. TAUTOMERISM OF THE CONDENSATION PRODUCT OF (−)−α-PHENYLETHYLAMINE AND ACETOACETIC ESTER

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Substances obtained by the reaction of organic amines with compounds showing keto-enol tautomerism are known to be capable of tautomerism, which in this case, is known as ketimide-enamine tautomerism.

The first case of this type of tautomerism was studied with β-aminocrotonic ester [1-3]. The basis of contemporary ideas on the structure of the reaction product of ammonia and acetoacetic ester was laid by Collie [4], who came to the conclusion that there is an equilibrium between ethyl β-aminocrotonate and ethyl β-iminobutyrate.

Various authors have used both chemical and physical methods to investigate the structure of ketimide-enamine systems. On the basis of refractometric data, Auwers and Susemihl [5] proposed that amino derivatives of β-dicarbonyl compounds have a predominantly enamine structure. They considered that the other form was only present as a trace. On the other hand, other authors [6, 7] considered that the ketimide form predominated on the basis of chemical reactions. The position of the equilibrium in a ketimide-enamine system (with β-aminocrotonic ester as the example) was determined by titration with bromine in various solvents [8], but the applicability of this method is doubtful [9]. Meanwhile, ketimide-enamine tautomerism has been studied much less than ketoenol tautomerism up to now.

We used the spectropolarimetric method to study ketimide-enamine tautomerism for the first time. The subject of the investigation was the condensation product of optically active (−) − α-phenylethylamine and acetoacetic ester. Even in the last century, Mohlau [10] observed the formation of two substances with m.p. 79-80° and 21° by the condensation of acetoacetic ester with benzylamine, which is the closest analog of α-phenylethylamine, but he did not investigate their structure. We condensed optically active α-phenylethylamine with acetoacetic ester under the conditions used by Mohlau. Different results were obtained, depending on the condensation temperature. Condensation at room temperature gave a liquid product, while condensation at −10 to −15° gave a solid crystalline substance as well as a liquid.

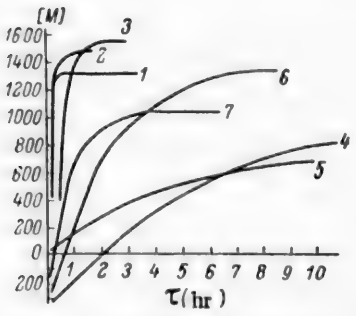


Fig. 1. Change in rotation of the crystalline form with time. 1) In dioxane; 2) in carbon tetrachloride; 3) in benzene; 4) in methanol; 5) in alcohol; 6) in ethyl acetate; 7) in a 65% solution of ethylene glycol in methanol.

The crystalline form of the condensation product melted at 64-78°; the melting point could not be determined accurately as the crystals were stable only at −10 to −15°. If they were stored at room temperature on an ordinary glass, the crystals changed to a liquid after 10-12 hr. Elementary analysis showed that the compositions of the crystalline and liquid parts of the condensation product were the same. Polarimetric measurements on the liquid part (Table 1) of the condensation product after separation of the crystals and the liquid obtained as a result of conversion of the crystals agreed well.

Thus, at the very beginning it was found that the reaction of (−)−α-phenylethylamine with acetoacetic ester yields two isomeric products, a solid and a liquid, and the former may be converted into the latter. It was necessary to determine the structures of the solid and liquid forms and the nature of their interconversion.

TABLE 1. Rotatory Dispersion of Liquid Form

λ mμ	Without solvent*		In benzene**		In methanol***		In acetic acid***		In pyridine*****	
			C 2.31		C 1.83		C 1.55		C 1.80	
	α****	[M]	α	[M]	α	[M]	α	[M]	α	[M]
690	—	—	—	—	—	—	−0.172	−25.85	+8.43	+1100
650	—	—	—	—	—	—	−0.007	−1.05	+7.35	+959.4
589	−34.75	−317.8	+1.42	+1340	+0.85	+1050	−0.025	−3.75	+8.93	+1170
578	−26.55	−242.8	+1.49	+1460	—	—	−0.105	−15.79	+9.03	+1180
566	−17.73	−162.1	—	—	—	—	—	—	—	—
554	−7.95	−72.71	—	—	—	—	—	—	—	—
546	−0.54	−5.00	+1.75	+1730	+0.98	+1210	−0.108	−16.24	+10.62	+1390
535	+12.33	+112.7	—	—	—	—	—	—	—	—
509	—	—	—	—	—	—	−0.124	−18.64	+13.24	+1730
493	+68.80	+629.2	—	—	—	—	—	—	—	—
466	—	—	—	—	—	—	−0.157	−23.60	—	—
436	+213.40	+1960	+3.77	+3700	+2.27	+2560	−0.212	−31.86	+23.08	+3010
420	+279.50	+2560	—	—	—	—	—	—	—	—
405	—	—	+5.14	+5040	+3.15	+3880	−0.260	−39.20	+31.84	+4150
365	—	—	+8.77	+8600	+5.46	+6740	−0.360	−54.36	+5.55**	+7030
334	—	—	+16.47	+16150	+10.68	+13150	−0.390	−59.40	+10.43	+13200
322	—	—	+17.60	+17300	+8.45	+10400	—	—	—	—
289	—	—	+8.87	+8700	—	—	—	—	+6.11	+7740

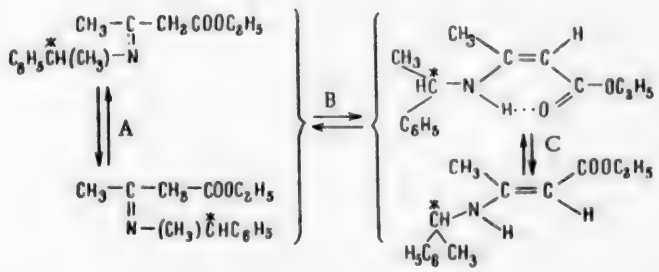
* Tube length 0.25 dm.

** Tube length 0.103 dm.

*** Tube length 1.00 dm.

**** Here and in all other cases, α is the angle read off.

In analogy with β-aminocrotonic ester, for which the tautomeric equilibrium has been studied [8] it could be expected that there would also be a ketimide-enamine equilibrium in β-(α-phenylethylamino)-crotonic ester. As the enamine form contains a double bond, cis-trans isomerism is quite possible and the cis-form would be expected to form an intramolecular hydrogen bond. It could be expected that this bond would be more or less clearly expressed, depending on the solvent. In addition, the ketimide could be in syn- and anti-forms. Thus, the following conversions are possible in the system studied:



Conversion A corresponds to syn-anti isomerism of the ketimide; conversion B corresponds to ketimide-enamine tautomerism; conversion C corresponds to cis-trans isomerism of the enamine. All these conversions should be reflected in the magnitude and nature of the optical rotatory dispersion.

A comparison of the optical rotation of the solid form (Table 2) with the rotation of substances of known structure could have solved the problem of the nature of the solid form. A change in rotation with time was observed with solutions of the solid form in all solvents (Fig. 1; see below for more details); however, in all cases the initial rotation or that extrapolated to zero time ($\tau = 0$) had a negative sign, i.e., the same sign as the rotation of the starting amine. The rotation of Schiff's bases obtained by condensation of acetaldehyde and isobutyraldehyde (Table 8) with optically active α-phenylethylamine has the same character. This gives grounds for drawing a preliminary conclusion that the solid form is similar in structure to a Schiff's base, i.e., is a ketimide.

TABLE 2. Rotatory Dispersion of Crystalline Form

$\lambda_{m\mu}$	In benzene* C 1.22		In methanol * C 1.93		In heptane** C 0.20		In dioxane ** C 0.30	
	α	[M]	α	[M]	α	[M]	α	[M]
650	+0.66	+1300	—	—	—	—	—	—
589	+0.73	+1440	+0.83	+1000	+1.13	+1340	+1.64	+1190
578	+0.84	+1660	+1.01	+1230	+1.16	+1350	+1.66	+1210
546	+0.98	+1930	+1.19	+1443	+1.37	+1600	+1.98	+1430
436	+2.01	+3970	+2.49	+3020	+2.97	+3460	+4.28	+3120
405	+2.76	+5450	+3.46	+4200	+4.08	+4760	+5.91	+4310
365	+4.67	+9230	+5.98	+7240	+0.38***	+8190	+0.55***	+7450
334	+9.08	+17900	+11.68	+14160	+0.67	+14500	+1.05	+14200
322	+12.31	+24300	+13.70	+16600	—	—	—	—
318	+9.01	+17800	+6.91	+8380	—	—	+1.70	+23000
297	+5.52	+10900	+6.74	+8170	+0.62	+13500	+0.83	+11300

* Tube length 0.103 dm.
** Tube length 1.00 dm.
*** Tube length 0.0538 dm.

It seems inprobable that the very strong change in molecular rotation observed (from −350° to +1000°) could have been produced by only one syn-anti conversion. It must be assumed that the gradual change in the rotation of solutions of the solid form is caused by the gradual conversion of the dissolved ketimide into the enamine. We should point out immediately that this idea is in agreement with the preferential existence of the enamine form, which is well known from the literature.

The most convincing demonstration of the power of our condensation products to show ketimide-enamine tautomerism is evidently the capacity of solutions of the crystalline and liquid condensation products in 65% aqueous methanol to give on standing solutions with the same molar rotation (Fig. 2, Table 1). This gives grounds for starting

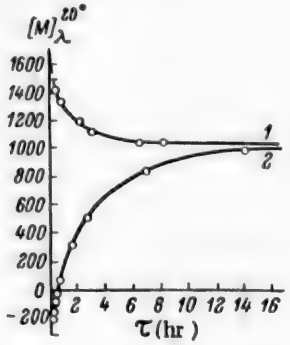


Fig. 2. Change in rotation in 65% methanol.
1) Liquid form; 2) crystalline form.

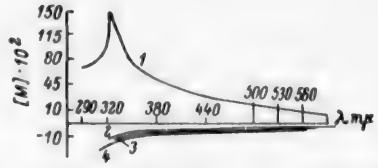


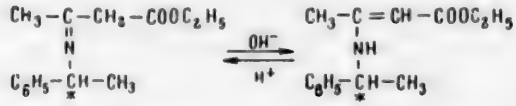
Fig. 3. Rotatory dispersion. 1) Liquid form in pyridine; 2) liquid form in acetic acid; 3) ethyl β-(α-phenylethylamino)-butyrate in acetic acid; 4) ethyl β-(α-phenylethylamino)-butyrate in pyridine.

that in this case we do not have a trans-cis conversion, which generally goes spontaneously in only one direction, but a system which shows ketimide-enamine tautomerism and is therefore capable of the reverse conversion. This conclusion is also confirmed by the results of observing the rate of change of rotation of solutions of the solid form in various solvents (Table 5). These results are given in Fig. 1.

The literature contains a series of views on the effect of solvents on tautomeric systems, which mainly refer to keto-enol tautomerism. A. N. Nesmeyanov and M. I. Kabachnik [11, 12] reported that the position of a tautomeric equilibrium depends in all cases on the relative basicity (or acidity) of the forms in the given medium. The equilibrium is always displaced toward the less basic (or, correspondingly, less acidic) form. In particular, this explains the predominance of the amino form in the β-aminocrotonic-iminoacetoacetic ester system.

Starting from this, we took solvents with opposite acid-base properties, namely, acetic acid and pyridine. We determined the optical rotatory dispersion of the liquid condensation product of (–)–α-phenylethylamine with acetoacetic ester and ethyl β-(α-phenylethylamino)-butyrate in these two solvents (Fig. 3). It was found that the liquid form of the condensation product of (–)–α-phenylethylamine and acetoacetic ester, which is capable of showing ketimide-enamine tautomerism, showed a sharp change in rotation both with respect to magnitude and sign with a change from a basic to an acidic solvent.

The sign remained the same for ethyl β-(α-phenylethylamino)-butyrate (Table 4) and there was no sharp difference in the magnitude of the rotation. This shows that the change in rotation in the first case is not merely the result of salt formation. This comparison gives grounds for concluding that the equilibrium of the system is displaced to the left under the action of an acidic agent and to the right under the action of a base.



In addition to the polarimetric measurements, for an additional demonstration of the existence of the enamine form, we also used the classical method of azo coupling, which Dimroth [13] applied to compounds capable of keto-enol tautomerism. We carried out the azo coupling of an alcohol solution of the crystalline form of the condensation

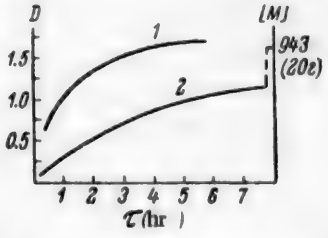


Fig. 4. Colorimetric determination of the coupling product of the crystalline form and sulfanilic acid (1) and change in rotation of a solution of the crystals in alcohol (2).

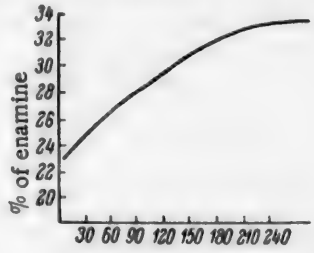


Fig. 5. Titration of a solution of crystals in alcohol with bromine.

product with diazosulfanilic acid and found the relation between the optical density of the dye formed and the time after solution (Fig. 4). For the same purpose, we also determined the change in the enamine content of an alcohol solution of the crystalline form with time by titration with bromine. The results of the experiments by three different methods, namely, spectropolarimetry, bromination, and azo coupling which are given as curves in Figs. 4 and 5, show that there is a gradual increase in the enamine content of the solution.

Thus, the results of azo coupling and bromination are in qualitative agreement with the results of polarimetric measurements, confirming that solutions of the crystalline form immediately after solution contain little of the enamine and that the amount of the latter gradually increases.

The enamine content in the equilibrium state may be calculated from the rotation of the equilibrium system, but this requires a knowledge of the rotations of the components of the system. The rotation of one of them, namely, the solid, ketimide form, is obtained readily by extrapolation to $\tau = 0$ of the curve of the change in rotation of the solid form in the corresponding solvent. This extrapolation for a solution in 65% aqueous methanol gives the value $[M]^{\text{liquid}}_{\lambda\ 578} = -350°$.

Analogously, from the curve in the change of rotation of the liquid form in 65% aqueous methanol, it was possible to find the rotation of the liquid form at zero time, $[M]^{\text{liquid}}_{\lambda 578} = +1600°$ (Table 6). However, in contrast to the case of the solid form, in this case it was not completely certain that the liquid isomer was a pure (enamine) form and not a mixture of ketimide and enamine forms of a mixture of cis- and trans-enamine forms. If it is assumed that the liquid form is wholly a geometrical isomer of the enamine, then from the values of the rotation given above, the enamine content of a 65% aqueous methanol solution in the equilibrium state is 68.4%.

TABLE 3. Rotatory Dispersion of β-(α-Phenylethylamino)-methylcrotonic Ester

λ mμ	Without solvent*		In methanol ** C 1.90		In benzene* C 1.52	
	α	[M]	α	[M]	α	[M]
690	+42.87	+1030	—	—	—	—
650	+47.63	+1140	—	—	—	—
589	+60.60	+1450	+0.58	+1470	+0.86	+1400
578	+64.37	+1550	+0.56	+1430	+0.88	+1430
546	+75.98	+1820	+0.57	+1440	+1.04	+1690
518	+90.26	+2166	—	—	—	—
455	+144.20	+3880	—	—	—	—
436	+172.25	+4120	+1.53	+3890	+2.35	+3790
405	+244.70	+5870	+2.19	+5370	+3.33	+5380
365	—	—	+4.12	+10500	+6.14	+9900
346	—	—	+5.96	+15100	+9.11	+14700
341	—	—	+5.62	+14280	+9.09	+14600
313	—	—	+3.88	+9850	+6.21	+10000

* Tube length 0.103 dm.
** Tube length 0.0538.

TABLE 4. Rotatory Dispersion of Ethyl β-(α-Phenylethylamino)-butyrate

λ mμ	Without solvent*		In pyridine** C 1.41		In acetic acid ** C 1.88	
	α	[M]	α	[M]	α	[M]
589	−4.20	−96.16	−0.60	−101.6	−0.35	−42.18
578	−4.40	−100.6	−0.64	−107.0	−0.41	−49.02
546	−4.93	−113.0	−0.70	−117.1	−0.44	−53.73
436	−8.22	−188.3	−1.18	−197.6	−0.79	−95.30
405	—	—	−1.38	−231.5	−0.96	−115.3
365	−12.46	−285.3	−1.75	−293.0	−1.25	−151.0
334	—	—	−2.16	−361.3	−1.63	−195.6
313	—	—	—	—	−1.98	−238.0

* Tube length 0.103 dm.
** Tube length 1.00 dm.

To confirm the structures of the solid and liquid forms of the condensation products, we investigated the infrared spectra of the two forms. It was found that the liquid form showed frequencies corresponding to free NH vibrations (3304 cm^{-1}) and bound NH vibrations (3220 cm^{-1}), which are characteristic of compounds with an intramolecular hydrogen bond. Thus, the infrared spectrum confirms the presence of the enamine in the liquid form of the condensation products with the enamine apparently in the form of both cis- and trans-isomers.

The infrared spectra of the solid form gave a less definite result. They also contain frequencies corresponding to NH vibrations. During the preparation of a paste in vaseline oil for measurements, there was apparently partial conversion of the ketimide into the enamine form; in this connection we should remember that according to polarimetric measurements, a similar conversion proceeds particularly rapidly in hydrocarbons (hexane). When the infrared spectrum of a solution of the solid form in carbon tetrachloride was plotted, a gradual increase in the intensity of the NH band with time was observed. This change is in agreement with the idea of the gradual conversion of the ketimide form into the enamine form; however, it is not certain that the observed increase in the intensity of the NH band was produced simply by an increase in concentration as a result of gradual evaporation of the solvent. This problem requires additional study as it is necessary to check the data of Schad [14], who assigned the structures of cis-trans isomers to the two forms of benzylaminocrotonic ester on the basis of infrared spectra.

In conclusion, we should note that we also condensed monomethylacetoacetic ester with α-phenylethylamine. It is found that the reaction did not occur under the conditions for the condensation of unsubstituted acetoacetic ester.

TABLE 5. Crystalline Form. In methanol. Sample 0.1965 g, solution volume 10.83 ml; tube length 1.00 dm; λ 578 mμ

Time (in min)	α	[M]	Time (in min)	α	[M]
0	—	—	293	+3.40	+412.4
10	−2.79	−338.5	383	+4.60	+557.2
15	−2.58	−313.0	438	+5.67	+688.4
20	−2.42	−293.3	558	+6.56	+795.4
45	−1.82	−221.1	618	+6.91	+837.9
60	−1.42	−172.9	1338	+8.73	+1059

Time (in min)	α	[M]	Time (in min)	α	[M]
104	−0.22	−26.93	1383	+8.75	+1062
138	+0.42	+51.65	1400	+8.75	+1062
163	+0.98	+119.3			
223	+2.33	+270.4			

In benzene. Sample 0.1225 g, solution volume 10.64 ml; tube length 0.50 dm; λ 578 mμ

0	—	—			
10	+1.23	+485.4	52	+3.58	+1414
17	+2.03	+801.5	122	+3.87	+1530
27	+2.79	+1101	182	+3.88	+1533
37	+3.23	+1274	207	+3.88	+1533

In dioxane. Sample 0.1600 g, solution volume 50.00 ml; tube length 1.00 dm, λ 578 mμ

Time (in min)	α	[M]	Time (in min)	α	[M]
0	—	—			
5	+0.79	+580.8	31	+1.78	+1300
8	+1.22	+893.3	54	+1.79	+1307
11	+1.46	+1068	89	+1.80	+1315
14	+1.58	+1153	100	+1.80	+1315

In 65% methanol. Sample 0.1186 g, solution volume 10.37 ml, tube length 2.00 dm, λ 578 mμ

Time (in min)	α	[M]	Time (in min)	α	[M]
0	—	—	108	+3.13	+319.0
13	−1.50	−153.2	170	+7.05	+515.3
23	−0.69	−70.53	420	+8.29	+845.9
30	−0.12	−12.54	1200	+9.70	+988.9
43	+0.72	+73.58	1260	+9.70	+988.9

In carbon tetrachloride. Sample 0.1391 g, solution volume 10.22 ml, tube length 1.00 dm, λ 578 mμ

Time (in min)	α	[M]	Time (in min)	α	[M]
0	—	—	25	+7.80	+1330
5	+2.79	+478.8	35	+8.25	+1415
10	+5.24	+898.0	52	+8.44	+1447
15	+6.43	+1100	80	+8.44	+1447

TABLE 6. Liquid Form. In 65% methanol. Sample 0.1160 g, solution volume 10.64 ml; tube length 1.00 dm; λ 578 mμ

Time (in min)	α	[M]	Time (in min)	α	[M]
0	—	—			
18	+6.45	+1420	165	+5.26	1126
35	+6.26	+1340	233	+5.16	1100
85	+5.80	+1240	480	+4.91	1050
120	+5.66	+1210	540	+4.91	1050

It occurred only with heating to 50°. These temperature conditions make it impossible to obtain two forms, as was the case in the condensation of unsubstituted acetoacetic ester.

EXPERIMENTAL

β-(α-Phenylethylamino)-crotonic ester. Condensation at room temperature. To 7.8 g of acetoacetic ester was added 7.26 g of (−) −α-phenylethylamine. The reaction mixture was left overnight at room temperature. The water liberated was removed in vacuum and the residue distilled. The yield was 11 g (80%).

B.p. 150-152° (1 mm), n^{20}_D 1.5474, d_4^{20} 1.0209, MR_D 72.26; calculated for ketimide 67.91, for enamine 68.05.

Found %: C 72.15; H 8.40; N 6.23. $C_{14}H_{19}O_2N$. Calculated %: C 72.25; H 8.18; N 6.00.

Condensation at −15°. With cooling in a cooling mixture and stirring, 3.63 g of (−) − α-phenylethylamine was added dropwise to 3.9 g of acetoacetic ester in 5 ml of ether in a quartz flask. The reaction mixture was left in the cold. After 1 hr, a finely crystalline precipitate formed and this changed to compact crystals after a day. The yield of crystals was 1.5 g and the m.p. 64-78°.

TABLE 7. Sample of 0.0742 g, Solution Volume 25.00 ml

Time (in min)*	Amount of solution (ml)	Optical density (D)
20	1.0	0.58
45	1.0	1.02
115	1.0	1.10
150	1.0	1.26
205	1.0	1.60
265	1.0	1.69

* Time from the moment of preparation of the solution until a sample was taken. Under analogous conditions we prepared the azo dye from a solution of the liquid form in 96% alcohol and diazosulfanilic acid. The sample weighed 0.0750 g, the solution volume was 25.00 ml, and the optical density (D) was 1.67.

The substance was sparingly soluble in heptane. When stored on a glass at room temperature, after 10-12 hr it had changed to a liquid with the same rotation as the condensation product obtained at room temperature (Table 1).

Found %: N 6.22. $C_{14}H_{19}O_2N$. Calculated %: N 6.00.

Rotatory Dispersion of Crystalline Form

The measurements were made after equilibrium had been established (5-24 hr after solution) (Table 2).

β-(α-Phenylethylamino)-methylcrotonic ester. A mixture of 2.88 g of methylacetoacetic ester and 2.42 g of (−)-α-phenylethylamine was heated on a water bath at 45-50° for 1 hr. The water liberated was removed in vacuum and the residue distilled. The yield was 2.8 g (60%). The rotatory dispersion is given in Table 3.

B.p. 150-154° (2 mm), n^{20}_D 1.5491, d_4^{20} 1.0306, MR_D 76.33; calculated for ketimide 72.53, for enamine 72.67.

Found %: N 5.96. $C_{15}H_{21}O_2N$. Calculated %: N 5.67.

Ethyl β-(α-Phenylethylamino)-butyrate. To a solution of 6.0 g of ethyl β-chlorobutyrate in 10 ml of alcohol were added 4.8 g of (−)-α-phenylethylamine and 2.4 g of sodium carbonate in 5 ml of water. The mixture was boiled for 2 hours. The precipitate of sodium carbonate gradually dissolved during the heating. The solution was filtered, the bulk of the alcohol removed by distillation, and an oil precipitated with water. The oil was extracted with ether and dried with potassium carbonate. The ether was removed and the oil distilled. The yield was 3.0 g (32%).

Rate of Establishment of Equilibrium in Solutions of β-(α-Phenylethylamino)-crotonic Ester (Tables 5 and 6)

TABLE 8. Rotatory Dispersion of the Schiff's Base From Isobutyraldehyde and (–)-α-Phenylethylamine

λ mμ	Without solvent*		In isooctane** C 5.41		In methanol* C 3.72	
	α	[M]	α	[M]	α	[M]
600	–19.6	–76.7	—	—	—	—
589	–23.8	–93.1	–0.122	–73.3	–2.045	–193.0
578	–25.0	–97.6	—	—	—	—
546	–28.3	–111.0	–0.148	–88.9	–2.353	–222.0
436	–49.7	–194.0	–0.242	–145.0	–4.467	–421.0
405	–60.6	–232.0	–0.294	–177.0	–5.551	–523.0
365	—	—	–0.384	–231.0	–7.692	–725.0
313	—	—	–0.583	–350.0	–12.13	–1144
302	—	—	–0.634	–381.0	—	—

* Tube length 0.50 dm.

** Tube length 0.0538 dm.

B.p. 140-143° (7 mm), n^{20}_D 1.4967, d_4^{20} 0.9970, MR_D 69.20; calc. 68.50.

Found %: N 6.31. $C_{14}H_{21}O_2N$. Calculated %: N 5.96.

Photocolorimetric Determination of Change in Light Absorption of Solution of Coupling Product of Crystalline Form with Diazosulfanilic Acid

Preparation of azo dye. To a sample of a solution of the crystalline form in 96% alcohol was added a suspension of diazosulfanilic acid; the mixture was made alkaline with 2 N sodium hydroxide solution. The light absorption (Table 7) was measured on an FEK-M photoelectric colorimeter.

Schiff's base from isobutyraldehyde and (–)-α-phenylethylamine. A mixture of 24 g of (–)-α-phenylethylamine, 18 ml of isobutyraldehyde, and 50 ml of benzene was boiled for 7 hr, the benzene and water removed, and the residue vacuum distilled. The yield was 22.8 g (65%). The rotatory dispersion is given in Table 8.

B.p. 88-90° (6-7 mm), d_4^{20} 0.8971, n^{20}_D 1.5017, MR_D 56.32; calc. 56.79.

Found %: N 7.94. $C_{12}H_{17}N$. Calculated %: N 7.99.

SUMMARY

1. It was established that the condensation of (–)-α-phenylethylamine with acetoacetic ester at low temperature yields a crystalline form with a ketimide structure and a liquid form, in which the enamine predominates.

2. The rate of conversion of the ketimide into the enamine form in various solvents was studied polarimetrically.

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INVESTIGATION OF THE HYDROGEN BOND IN CHOLINOLYTIC SUBSTANCES BY MEANS OF INFRARED ABSORPTION SPECTRA. II

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It has been suggested that the hydroxyl group in the molecule of atropine and some of its synthetic substitutes playes an important part in the mechanism of their physiological (cholinolytic) action. It is considered that if forms a hydrogen bond with one of the active centers of the corresponding biochemical system of the organism [1]. It might be expected that the difference in the physiological activity of such cholinolytic substances is connected to a certain extent with the difference in the properties of their hydroxyl groups. As the state of the hydroxyl may be assessed from vibration spectra, we undertook an investigation of the spectra of a series of hydroxyl-containing cholinolytic substances. In the first communication [2], the infrared absorption spectra of 2-diethylaminoethyl esters of diphenylacetic and benzilic acids and 1,1-diphenyl-2-(β-diethylaminoethoxy)-ethanol-1 were examined.

In the present communication we give the results of investigating a considerable number of new subjects and more accurate data for the substances studied previously (Table 1). For comparison, we also investigated two substances which do not contain amino groups and do not have cholinolytic properties.

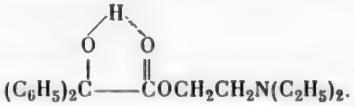
EXPERIMENTAL

The substances required for the investigation were synthesized by methods described in the literature and purified until the properties were constant either by recrystallization or by vacuum distillation.

We studied 0.02 M solutions of the free bases in carbon tetrachloride. The absence of appreciable association under these conditions was indicated by the fact that the spectra did not change when the concentration of the substance was reduced by a factor of 5-10 with a simultaneous increase in the layer thickness. The spectra were plotted on an IKS-14 infrared spectrometer with an LiF prism in the region of 2.7-3.2 μ and for some substances, with an NaCl prism in the region of 5.6-6.4 μ.* The data obtained are given in Figs. 1 and 2 and in Table 2.

DISCUSSION OF RESULTS

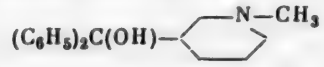
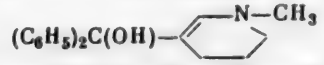
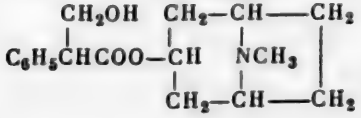
As Fig. 1 (curve 1) shows, the hydroxyl group of the 2-diethylaminoethyl ester of benzilic acid (II) gives a main absorption peak at 2.83 μ and an additional peak at 2.77 μ. We did not observe the latter peak previously. Undoubtedly, it should be ascribed to the vibration of the free hydroxyl. The first peak is apparently connected with the vibration of the hydroxyl in a weak intramolecular hydrogen bond. There is an analogous picture in the case of the methyl ester of benzilic acid (IV) (Fig. 1, 2), which makes it possible to exclude the participation of the amino group of compound (II) in such an intramolecular bond. It is most probable that the carbonyl oxygen is involved in this bond:



This is confirmed by the displacement of the absorption maximum of the carbonyl in this compound toward longer wavelengths in comparison with compound (I) (Table 2). This displacement is evidently not connected with

* We are very grateful to N. V. Mikhailova for plotting the spectra and to V. N. Nikitin for help in their interpretation.

TABLE 1. Physicochemical Constants and Cholinolytic Activity of Substances Investigated

Compound No.	Compound	Empirical formula	Melting point		Boiling point of base (pressure in mm)	Relative cholinolytic activity
			hydrochloride	base*		
I	$(C_6H_5)_2CHCOOCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{25}O_2N$	115—116°	n_D^{20} 1.5379	165°(1)	0.002
II	$(C_6H_5)_2C(OH)COOCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{25}O_3N$	177—178	53—55°	—	0.143
III	$(C_6H_5)_2C(OCH_3)COOCH_2CH_2N(C_2H_5)_2$	$C_{21}H_{27}H_3N$	138—139	n_D^{20} 1.5348	151 (0.01)	0.002
IV	$(C_6H_5)_2C(OH)COOCH_3$	$C_{15}H_{14}O_3$	—	74—75°	165 (5)	—
V	$(C_6H_5)_2CHCOSCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{25}ONS$	124—125	35—36	—	0.007
VI	$(C_6H_5)_2C(OH)COSCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{25}O_2NS$	143.5—144.5	113.5—114.5	—	0.25
VII	$(C_6H_5)_2CHCONHCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{26}ON_2$	143—144	95—95.5	—	<0.001
VIII	$(C_6H_5)_2C(OH)CONHCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{26}O_2N_2$	175.5—176.5	105—196	—	0.003
IX	$(C_6H_5)_2C(OH)CON(CH_3)CH_2CH_2N(C_2H_5)_2$	$C_{21}H_{28}O_2N_2$	155.5—156	n_D^{20} 1.5578	—	0.03
X	$(C_6H_5)_2C(OH)CH_2OCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{27}O_2N$	181—182	55.5—56.5°	135 (0.01)	0.001
XI	$(C_6H_5)_2C(OH)CH_2SCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{27}ONS$	134.5—135	53—54	—	0.003
XII	$(C_6H_5)_2C(OH)CH_2OCH_2CH_3$	$C_{16}H_{18}O_2$	—	n_D^{20} 1.5665	148.5 (2.5)	—
XIII	$(C_6H_5)_2C(OH)CH_2CH_2N(C_2H_5)_2$	$C_{19}H_{25}ON$	204.5—205.5	53.5—54.5°	—	0.014
XIV	$(C_6H_5)_2C(OH)CH_2CH_2CH_2CH_2N(C_2H_5)_2$	$C_{21}H_{29}ON$	175—176	80—80.5	—	0.006
XV		$C_{19}H_{23}ON$	232	146.7—147.3	—	0.001
XVI		$C_{19}H_{21}ON$	222.5—223	188.5—189.5	—	0.006
XVII		$C_{17}H_{23}O_3N$	165—166	115—116	—	1.0

* The refractive index is given for liquids.

the inductive effect of the hydroxyl oxygen as it is absent in the case of compound (III) (Table 2). Other authors [3, 4] have also suggested that a weak intramolecular hydrogen bond of the above type is formed in esters of α-hydroxy acids. The low strength of the bond in this case may be explained by the great distance between the hydrogen and oxygen atoms.

With a change from compound (II) to the analogous thioester (VI), one might expect even greater weakening of the hydrogen bond between the hydroxyl group and the carbonyl because of the decrease in the negative charge

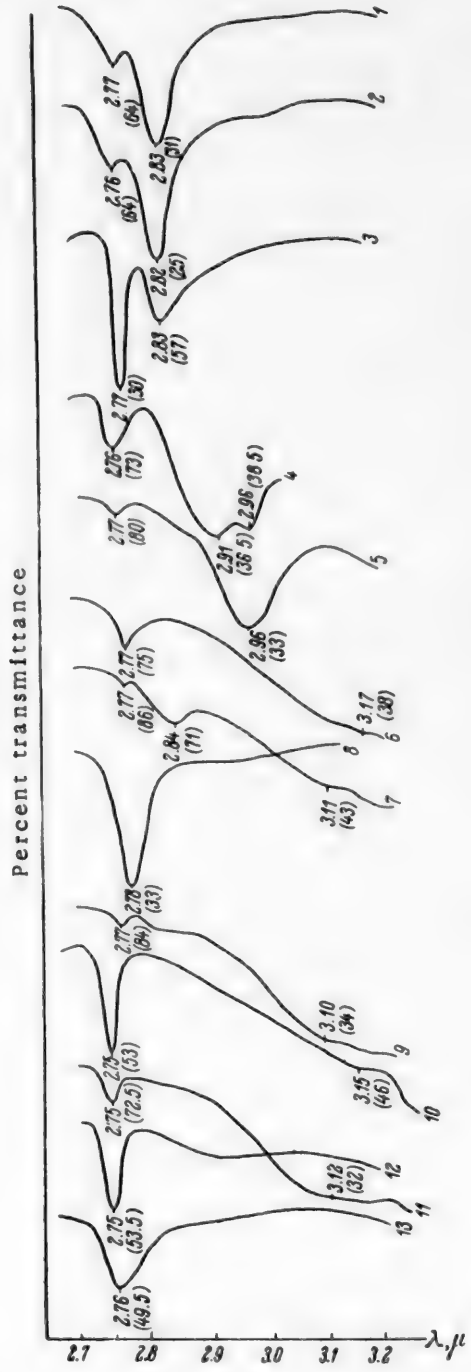
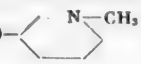
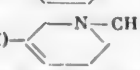
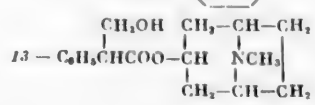


TABLE 2

Compound	Position of absorption maxima in the region of carbonyl valence vibrations (λ in μ)
I	5.75
II	5.81
III	5.75
V	5.92
VI	5.93 and 6.01
VII	5.97
VIII	5.97
XVII	5.81

on the oxygen of the latter. In actual fact, although the hydroxyl absorption peak in the spectrum of this substance (Fig. 1, 3) divided into two to form two maxima (2.77 and 2.83 μ), the first of these, which corresponds to the free hydroxyl, was much more intense. The bulk of the molecules of this substance apparently contain a free hydroxyl and only a comparatively small number have the hydroxyl bound with a weak intramolecular bond. The nature of the spectrum of this compound in the region of carbonyl valence vibrations was also in accordance with this conclusion (Table 2, Fig. 2). The carbonyl absorption band in this case had two maxima (5.93 and 6.01 μ).

Fig. 1. Infrared transmission spectra in the region of the main hydroxyl valence vibrations of the following compounds:

1 — $(C_6H_5)_2C(OH)COOCH_2CH_2N(C_2H_5)_2$,
2 — $(C_6H_5)_2C(OH)COOCH_3$,
3 — $(C_6H_5)_2C(OH)COSCH_2CH_2N(C_2H_5)_2$,
4 — $(C_6H_5)_2C(OH)CONHCH_2CH_2N(C_2H_5)_2$,
5 — $(C_6H_5)_2C(OH)CON(CH_3)CH_2CH_2N(C_2H_5)_2$,
6 — $(C_6H_5)_2C(OH)CH_2OCH_2CH_2N(C_2H_5)_2$,
7 — $(C_6H_5)_2C(OH)CH_2SCH_2CH_2N(C_2H_5)_2$,
8 — $(C_6H_5)_2C(OH)CH_2OCH_2CH_3$,
9 — $(C_6H_5)_2C(OH)CH_2CH_2N(C_2H_5)_2$,
10 — $(C_6H_5)_2C(OH)CH_2CH_2CH_2CH_2N(C_2H_5)_2$,
11 — $(C_6H_5)_2C(OH)$—  ,
12 — $(C_6H_5)_2C(OH)$—  ,
13 — 

The first of these, which was most intense, most probably corresponds to the undisturbed carbonyl vibration as it is in almost the same position as in the spectrum of the analogous thioester (V), which does not contain a hydroxyl group (Table 2). The second maximum (6.01 μ) should correspond to the vibration of a carbonyl disturbed by the formation of a hydrogen bond with the hydroxyl.

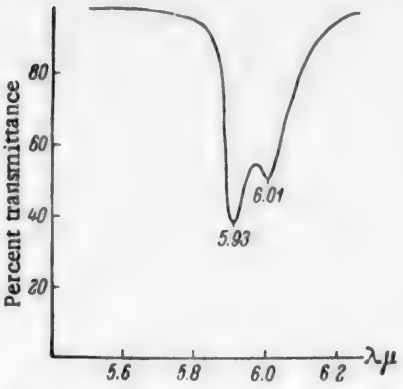
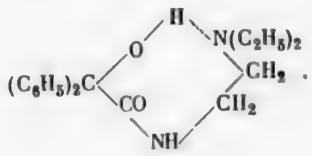


Fig. 2. Infrared transmission spectra of the compound $(C_6H_5)_2C(OH)COSCH_2CH_2N(C_2H_5)_2$ in the region of the main carbonyl valence vibrations.

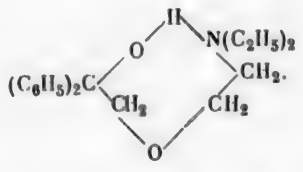
The spectrum of the 2-diethylaminoethylamide of benzilic acid (VIII) (Fig. 1, 4) had a more complex structure than the previous ones. One of the three absorption maxima (2.19 μ) should be assigned to the vibration of an undisturbed N – H bond as this maximum was absent from the spectrum of the analogous disubstituted amide (IX) (Fig. 1, 5). The weak maximum (2.77 μ) must correspond to the vibration of the free hydroxyl and the much more intense maximum (2.96 μ) to the hydroxyl bound in a quite strong intramolecular hydrogen bond. This bond is evidently formed through the nitrogen of the amino group and not the oxygen of the carbonyl, as the absorption maximum of the latter in this compound has exactly the same position as the carbonyl absorption maximum of the amide (VII), which does not contain a hydroxyl group (Table 2). A considerable number of the molecules of the amide (VIII) evidently exist in the cyclic form:



The spectrum of the N-methyl-N-(2-diethylaminoethyl)-amide of benzilic acid (IX) (Fig. 1, 5) is similar in many ways to the spectrum of compound (VIII). It only lacks the maximum of N – H vibrations and the free hydroxyl peak is less intense. It may be assumed that the amide (IX) has an intramolecular hydrogen bond similar to that in the amide (VIII).

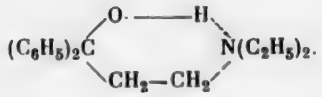
The spectrum of 1,1-diphenyl-2-(β-diethylaminoethoxy)-ethanol-1 (X) (Fig. 1, 6) has a very different character. Together with a comparatively small free hydroxyl peak (2.77 μ), the spectrum of this compound has a broad and intense absorption band, beginning at ~2.85 μ and merging with the region of C – H vibrations so that the absorption maximum is difficult to determine. It lies at approximately 3.17 μ. This type of absorption corresponds to a hydroxyl involved in a very strong hydrogen bond. As the investigation was carried out with a dilute solution, this bond can only be intramolecular. The spectrum of the sulfide (XI) (Fig. 1, 7) is similar in character to that of the analogous ether (X). The only difference is that the free hydroxyl band has two maxima. On this basis it can be assumed that in compound (XI) also the hydroxyl is involved in a very strong intramolecular hydrogen bond.

As only one absorption maximum corresponding to the free hydroxyl group was found in the spectrum of 1,1-diphenyl-2-ethoxyethanol-1 (XII) (Fig. 1, 8), it can be stated that in compound (X), the intramolecular hydrogen bond is formed between the hydroxyl and the amino group nitrogen and not the ether oxygen, as we assumed previously [2]. Here, as in the case of amides of benzilic acid (VIII and IX), the bulk of the molecules must form rings.



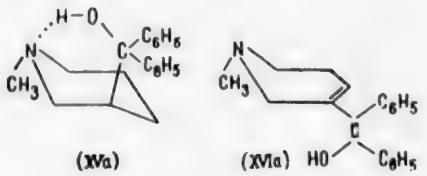
However, judging by the nature of the spectrum, the hydrogen bond here must be much stronger.

A very strong intramolecular hydrogen bond is also formed through the hydroxyl and the amino group in 1,1-diphenyl-3-diethylaminopropanol-1 (XIII). In the spectrum of this substance (Fig. 1, 9), we found only a weak hint of the presence of a free hydroxyl and then there was a broad absorption band with a maximum at ~3.1 μ. It should be noted that an analogous picture was found [5] in the case of diastereoisomeric 1,3-dimethyl-1-phenyl-3-(N-piperidyl)-propanols-1. The particular strength of the hydrogen bonds in these cases is probably caused by the formation of a six-membered ring.



With lengthening of the carbon chain between the nitrogen and hydroxyl to five atoms, the possibility of the formation of such a cyclic form is decreased. This is evidently why the spectrum of 1,1-diphenyl-5-diethylamino-pentanol-1 (XIV) (Fig. 1, 10) shows a clear peak of a free hydroxyl (2.75 μ) with considerable retention of the broad absorption band in the region of 2.8-3.15 μ, corresponding to a strong intramolecular hydrogen bond.

It is noteworthy that there is a considerable difference between the spectra of two substances which are similar in structure, namely, 1-methyl-3-diphenylmethylolpiperidine (XV) and 1-methyl-3-diphenylmethylolpiperidiene-3 (XVI). The spectrum of the former (Fig. 1, 11) is very similar to that of compound (XIII) and indicates that its molecule contains a strong intramolecular hydrogen bond, which can be formed only through the hydroxyl and the nitrogen of the piperidine ring (XVa). The spectrum of compound (XVI) (Fig. 1, 12) was found to contain vibrations of only a free hydroxyl in accordance with the configuration of the molecule of this compound, which excludes the possibility of formation of an intramolecular hydrogen bond (XVIa).



(XVa) (XVIa)

Finally, the spectrum of the base atropine (XVII) (Fig. 1, 13) has the band of a free hydroxyl, which is considerably wider than for a primary aliphatic alcohol. It may be assumed that the vibration of the hydroxyl group of atropine is somewhat disturbed by its weak intramolecular interaction with the carbonyl oxygen in the same wa as in compound (II). This conclusion is confirmed by the identical positions of the absorption maxima of the carbonyl groups of these compounds (Table 2).

Thus, in the hydroxyl-containing cholinolytic substances examined, the hydroxyl group is in different states and shows different tendencies to form an intramolecular hydrogen bond either with a carbonyl oxygen or with the nitrogen of an amino group. As a result of this intramolecular interaction, many of these substances should exist in solution in some forms of cyclic conformation with different degrees of stability. The hydroxyl groups of these cholinolytic substances should differ strongly from each other in their capacity to form intermolecular hydrogen bonds, which may affect their capacity to react with corresponding biochemical systems of the organism.

The hydroxyl group is known to be only one of the factors influencing the cholinolytic activity of a substance. Even substances without a hydroxyl have a cholinolytic action, as is shown, for example, by the data given in Table 1. Therefore, one cannot expect to find a direct relation between the cholinolytic activity and the state of the hydroxyl in the substances examined, which differ quite strongly in chemical structure in a number of cases. However, this relation may be found to a certain extent on examining the most similar substances, such as (II), (VI), (VIII), (IX), (X), (XI), and (XIV). It is necessary to exclude (VIII) from this series as monosubstituted aminoalkylamides of this type are known to have an anomalously low cholinolytic activity in the case of the most diverse acids, including those not containing a hydroxyl. The remaining substances may be arranged in the following order with respect to falling cholinolytic activity: (VI) > (II) > (IX) > (XIV) > (XI) > (X) (Table 1). As has been shown above, the capacity of these substances to form an intramolecular hydrogen bond increases in precisely this sequence. It is only in the case of compounds (X) and (XI) that this capacity is practically the same according to the spectra. Thus, the cholinolytic activity of these compounds depends on how "free" their hydroxyl groups are.

A good example of this relation is provided by substances (XV) and (XVI), of which the former contains a hydroxyl held in a strong intramolecular bond and shows only weak cholinolytic properties, while in the latter, the hydroxyl group is "free," which evidently is responsible for its quite high cholinolytic activity.

In atropine, which is known to be one of the most powerful cholinolytic substances, the hydroxyl group is also quite "free." However, a closer comparison of this alkaloid with the substances examined above is impossible because of the considerable difference in their chemical structures. The discrepancy between the cholinolytic activity and the degree of "freedom" of the hydroxyl of substances (XIII) and (XIV) can be assumed to be caused not only by the difference in the state of the hydroxyl, but, to a much greater extent, by the difference in the length of the main chain of the molecule, which is known to play a substantial part in the mechanism of the physiological action of cholinolytic substances. A comparison of the cholinolytic activity of these two substances, especially with allowance for the greater "freedom" of the hydroxyl in compound (XIV), indicates the disadvantage of a chain of five atoms.

All this gives grounds for recommending that not only the presence, but also the state of the hydroxyl group should be considered in discussing the relation between chemical structure and physiological action among cholinolytic substances.

SUMMARY

1. The infrared absorption spectra of thirteen cholinolytic and two model substances in carbon tetrachloride were plotted in the region of 2.7-3.2 μ and those of eight substances in the region of 5.5-6.4 μ.

2. It was established that in some hydroxyl-containing cholinolytic substances, the hydroxyl group is held in intramolecular hydrogen bonds of different strengths either with a carbonyl oxygen or with the nitrogen of an amino group.

3. It was shown that a comparison of cholinolytic substances containing a hydroxyl group which are similar in chemical structure reveals a relation between the physiological activity and the state of the hydroxyl group.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

RATE OF ACETYLATION OF SOME CHOLINOLYTIC SUBSTANCES CONTAINING A HYDROXYL GROUP

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Original article submitted July 15, 1960

By means of infrared spectroscopy, one of us [1] established recently that among atropine-like cholinolytic substances which are aminoalkyl esters, thioesters, and amides of hydroxy acids and also amino alcohols, the hydroxyl group is capable of forming an intramolecular hydrogen bond either with a carbonyl oxygen or with the nitrogen of an amino group and that this capacity is expressed to different extents in different compounds. It was shown that the highest physiological activity is characteristic of substances containing a free hydroxyl group, which is capable of forming intermolecular hydrogen bonds. The participation of the hydroxyl in an intramolecular hydrogen bond leads to a greater reduction in the cholinolytic activity, the stronger this bond is.

However, these data are only of a qualitative nature. To obtain comparable quantiative data, we undertook an investigation of the reactivity of the hydroxyl in various cholinolytic substances, in particular, its capacity for acetylation by acetyl chloride. We assumed that the reactivity of the hydroxyl, like its capacity to form intermolecular hydrogen bonds, depends on the lability of the hydrogen atom and that these two properties should change in parallel to some extent. The relation between the reactivity of a hydroxyl and its participation in an intramolecular hydrogen bond is widely known. This phenomenon has been demonstrated, in particular, on the acylation of hydroxyl-containing compounds [2-4]. Hudson and Stelzer [5] consider that alcohols can associate with acyl chlorides through the carbonyl group of the latter to form complexes with the composition $R'COCl(ROH)_i$. In the opinion of these authors, the capacity of alcohols for acylation increases with an increase in their capacity for association.

To study acetylation by acetyl chloride, we used 12 cholinolytic and 4 model substances (Tables 1 and 2). The infrared absorption spectra of most of these substances were plotted previously [1]. The acetylation method made it possible to investigate not only the free bases of cholinolytic substances, but also the hydrochlorides and most of their quaternary ammonium salts. In this respect, the given method has great advantages over the spectroscopic and cryoscopic methods, which cannot be used to investigate the latter because of the very low solubility of salts in carbon tetrachloride and benzene. The investigation of these salts is of great interest as the state of the hydroxyl group in them may be different from that in free bases.

EXPERIMENTAL

The substances required for the investigation were synthesized by known methods and purified until their physical properties were constant. The acetylation was carried out at 30° in chloroform containing 0.04 mole of the hydroxyl-containing compound acetylated and 0.005 mole of acetyl chloride.*

The rate of acetylation of the free bases of the cholinolytic substances was determined by a colorimetric method of determined alkaloids [6], which is based on the capacity of free bases of the latter to form chloroform-soluble colored complexes with Methyl Orange. The hydrogen chloride liberated as a result of acetylation binds part of the amino alcohol investigated so that the amount of complex with Methyl Orange extracted is reduced. The calculations were made with the formula for the rate of a bimolecular reaction, proceeding with different concentrations of the components:

$$K_{2,t} = \frac{1}{a-b} \cdot \ln \frac{b(a-x)}{a(b-x)},$$

* Dilute solutions were used because this reduced the probability of intermolecular association and also because a number of the salts were difficultly soluble in chloroform.

TABLE 1. Model Substances

Compound No.	Compound	Boiling point (pressure in mm)	Melting point*	Acetylation constant K_a (liter/mole · min)
I	$(C_6H_5)_2C(OH)COOC_2H_5$	157—158° (3)	33—34°	1.38
II	$(C_6H_5)_2C(OH)CH_2OC_2H_5$	148.5 (2.5)	n_D 1.5665	0.50
III	$(C_6H_5)_2C(OH)C_2H_5$	152—153 (5)	94—95	0.50
IV	$(C_6H_5)_2C(OH)C{\equiv}CH$	145—147 (3)	47.5—49	1.73

* The refractive index is given for liquids.

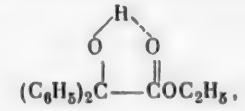
where a and b are the concentrations of the amino alcohol and acetyl chloride, respectively, x is the change in concentration determined from the change in optical density after time t.

For determination of the rate of acetylation of hydrochlorides and quaternary salts, a sample of the hydroxyl-containing substance investigated was dissolved in anhydrous chloroform and then the required amount of acetyl chloride added. Samples were taken after definite time intervals and the hydrogen chloride liberated was titrated with a 0.5 N solution of triethylamine in toluene in the presence of a mixed indicator (Methyl Red and Methylene Blue) [5, 7]. The formula given above was used for the calculations. In several cases it was impossible to determine the acetylation rate at the choosen concentration because of the low solubility of the quaternary salts (Tables 1 and 2).

DISCUSSION OF RESULTS

The data presented in Table 1 show that the hydroxyl of the diphenylmethylol group reacts with acetyl chloride at different rates, depending on the nature of the radical to which this group is attached. These rates are low (and practically identical) in the case of the two electron-donor substituents C_2H_5 and $CH_2OC_2H_5$.

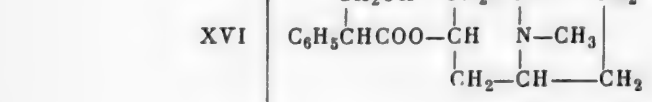
In the case of the carbethoxyl group, the reactivity of the hydroxyl is strongly increased as a result of the electron-attracting action of this group. It is probably for the same reason that there is an even greater increase in the reactivity of the hydroxyl when an ethynyl group is introduced. The somewhat weaker effect of the carboethoxyl group is probably connected with the presence of a weak intramolecular hydrogen bond of the following type:



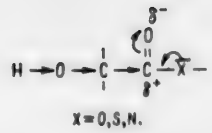
whose formation in the case of benzilic esters was confirmed previously [1].

An examination of the data presented in Table 2 shows that the picture is much more complicated when an amino group is introduced into the molecule of the hydroxyl-containing substance. The reactivity of the hydroxyl of the diphenylmethylol group then increases in most cases. The reactivity of the hydroxyl depends on the state of the amino group (base, hydrochloride, or quaternary salt) and also on the size of the substituents at the nitrogen. The considerable increase in the acetylation rate with a change from the ethyl ester of benzilic acid (Table 1, compound (1)] to its diethylamino derivative [Table 2, compound (VI)] may be explained by the catalytic action of the free amino group. The relation of the acetylation rate to the magnitude of the substituents at the nitrogen [Table 2, compounds (V), (VI), and (VII)] also indicates the direct participation of the amino group in the acetylation of the hydroxyl. With a change from the ester (VI) to the corresponding thioester [Table 2, compound (VIII)], the acetylation rate increases sharply and with a change to the corresponding amides [Table 2, compounds (IX) and (X)], it falls appreciably. These data are in complete agreement with the fact established by infrared spectra [1] that the hydroxyl in compound (VIII) is less firmly bound, while those in compounds (IX) and (X) are more firmly bound by an intramolecular hydrogen bond than in compound (VI). We cannot deny the possibility of some induction effect on the lability of the hydrogen of the hydroxyl group from the electron deficit at the carbonyl carbon, which differs in magnitude for esters, thioesters, and amides.

TABLE 2. Cholinolytic Substances

Compound No.	Compound	Empirical formula	Melting point			Relative cholinolytic activity		K_2 of acetylation (liter/mole · min)		
			base[a]	hydrochloride	iodomethylate	hydrochloride	iodomethylate	base	hydrochloride	iodomethylate
V	$(C_6H_5)_2C(OH)COOCH_2CH_2N(CH_3)_2$	$C_{18}H_{21}O_3N$	99.5—101°	187—188°	193.5—194.5°	0.067	0.67	2.68	1.84	b
VI	$(C_6H_5)_2C(OH)COOCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{25}O_3N$	53—55	177—178	140—141	0.143	2.0	2.42	1.71	1.72
VII	$(C_6H_5)_2C(OH)COOCH_2CH_2N(C_4H_9)_2$	$C_{24}H_{33}O_3N$		126—127	85—86	0.001	0.001	2.19	1.44	1.71
VIII	$(C_6H_5)_2C(OH)COSCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{25}O_2NS$	113.5—114.5	143.5—144.5	156—157	0.25	0.33	9	3 68	b
IX	$(C_6H_5)_2C(OH)CONHCH_2CH_2N(C_2H_5)_2$	$C_{20}H_{26}O_2N_2$	105—106	175.5—176.5	202—203[c]	0.003	0.007	1.50	1.50	1.55[c]
X	$(C_6H_5)_2C(OH)CON(CH_3)CH_2CH_2N(C_2H_5)_2$	$C_{21}H_{28}O_2N_2$	n_D^{20} 1.5578	155.5—156	221—222 (decomp.)[c]	0.03	0.33[c]	1.90	1.43	1.53[c]
XI	$(C_6H_5)_2C(OH)CH_2OCH_2CH_2N(C_2H_5)_5$	$C_{20}H_{27}O_2N$	55.5—56.5	181—182	123—124.5	0.001	0.007	0.29	0.14	0.30
XII	$(C_6H_5)_2C(OH)CH_2CH_2N(C_2H_5)_2$	$C_{19}H_{25}ON$	53.5—54.5	204.5—205.5	227—228 (decomp.)[c]	0.014	0.143[c]	0.35	0.18	0.33 c
XIII	$(C_6H_5)_2C(OH)CH_2CH_2CH_2CH_2N(C_2H_5)_2$	$C_{21}H_{29}ON$	80—80.5	175—176	198—198.5	0.006	0.01	0.94	0.61	b
XIV	$(C_6H_5)_2C(OH)C{\equiv}CCH_2N(C_2H_5)_2$	$C_{20}H_{23}ON$	96.5—97.5	174.5—175	158—160	0.025	0.22	1.80	1.78	1.75
XV	$(C_6H_5)_2C(OH)C{\equiv}CCH_2CH_2N(C_2H_5)_2$	$C_{21}H_{25}ON$	103—104	176 (decomp.)	194	0.02	0.17	1.92	1.27	b
XVI		$C_{17}H_{23}O_3N$	115—116	165—166	177—178	1.0	10.0	5.56	2.60	b

Footnote. [a]The refractive index is given for liquids. [b]The determination could not be carried out because of the low solubility of the salt. [c]The data refer to the bromoethylate.



X=O,S,N.

The magnitude of this deficit should evidently depend inversely on the capacity of the p-electrons of the atoms X for conjugation with the π-bond. The atoms examined should lie in the following order with respect to this capacity: S < O < N. On this basis one can expect a gradual fall in the lability of the hydrogen atom of the hydroxyl group and a decrease in its acetylation rate in the sequence of compounds (VIII), (VI), (IX), or (X), which agrees with experimental facts.

In contrast to the ethyl ester of benzilic acid (I), the introduction of a diethylamino group into compounds (II) and (III) (Table 1) did not lead to an increase in the reactivity of the hydroxyl. The data given in Table 2 [compounds (XI) and (XII)] show that the reactivity even fell appreciably. We consider that the reason for this is the formation of a very strong intramolecular hydrogen bond between the hydroxyl and the amino group, as was demonstrated by means of infrared spectra [1]. The weakening of this bond observed with a change from compound (XII) to compound (XIII) (Table 2) leads to an increase in the reactivity of the hydroxyl. In the case of the acetylenic amino alcohol (XIV), no appreciable change in the reactivity of the hydroxyl is observed in comparison with diphenylethynylcarbinol (VI) as here the structure of the molecule excludes the intramolecular interaction of the hydroxyl and amino groups.

The possibility of intramolecular interaction of the hydroxyl and amino groups increases with a change to the next acetylenic amino alcohol (XV). In this case, the amino group shows some catalytic action. Finally, the alcohol group of atropine is acetylated at a very high rate, firstly because it is primary and secondly, because its intramolecular hydrogen bond with the carbonyl oxygen is weak [1].

With a change from the free bases of cholinolytic substances to their hydrochlorides, in almost all cases (with two exceptions) there is a fall in the reactivity of the hydroxyl, sometimes to a considerable extent. We regard this as confirmation of the catalytic role of the free amino group in acetylation of the hydroxyl.

The disappearance of the catalytic properties in the case of hydrochlorides and quaternary ammonium salts may be connected with their inability to form complexes with acyl chlorides. It is still not clear why there is no difference in the reactivities of the hydroxyls in the hydrochloride and the base of the diethylaminoethylamide of benzilic acid (IX). The absence of this difference with 1,1-diphenyl-4-diethylaminobutyn-2-ol-1 (XIV) is understandable as its amino group cannot have an intramolecular catalytic effect even in the unprotonized state.

With most quaternary ammonium salts which could be investigated, the reactivity of the hydroxyl was found to be of approximately the same order as with the corresponding hydrochlorides. The exceptions are the two substances (XI) and (XII), which, in the form of the free bases, are capable of forming a particularly strong intramolecular hydrogen bond with the nitrogen of the amino group. In these two cases, the reactivity of the hydroxyl group of the quaternary ammonium salts was considerably higher than that of the hydrochlorides. This may be explained by the fact that the latter retain the capacity to form an intramolecular hydrogen bond, while the quaternary ammonium salts do not. Even in the hydrochlorides of the dialkylaminoethyl esters of benzilic acid (V), (VI), and (VII), there is evidently some interaction between the hydroxyl and the ammonium group as a definite relation is observed between the acetylation rate of the hydrochlorides of these amino esters and the magnitude of the substituents at the nitrogen atom.

In addition to the hydroxyl group, other structural characteristics of the substance, in particular, the length of the main chain of the molecule, the substituents at the nitrogen and the carbinol carbon, etc. are known to have no less important effect on the cholinolytic activity. Therefore, to compare the kinetic data obtained with the cholinolytic activity, it is necessary to choose only those compounds which are closest in chemical structure, namely, (VI), (VIII), (X), (XI), (XIII), and (XV).

As the data in Table 2 show, in this series there is a clear correspondence between the cholinolytic activity and the rate of acetylation of the hydroxyl group of the compound.

Of the substances which are not in this series, we should mention atropine, which has a high cholinolytic activity and also shows a high capacity for acetylation.

Considering that the capacity of the hydroxyl group for acetylation depends on the lability of the hydrogen atom, which is also connected closely with its capacity to form intermolecular hydrogen bonds, we regard the results obtained as confirmation of the hypothesis on the relation between the cholinolytic activity of hydroxyl-containing substances and their capacity to form intermolecular hydrogen bonds through the hydroxyl.

SUMMARY

1. An investigation was made of the rate of acetylation by acetyl chloride of twelve cholinolytic substances containing a hydroxyl and an amino group and four model substances which do not contain an amino group. The free bases, hydrochlorides, and some quaternary ammonium salts of the cholinolytic substances were acetylated.

2. It was established that the reactivity of the hydroxyl group in the substances investigated with respect to acetyl chloride falls when the group is involved in an intramolecular hydrogen bond and increases under the action of electron-attracting atoms and groups in the radical attached to the carbinol group.

3. It was established that the amino group in the cholinolytic substances investigated has a substantial effect on the reactivity of the hydroxyl. The hypothesis was put forward that the unprotonized amino group has an intramolecular catalytic action in the acetylation of hydroxyl-containing cholinolytic substances by acetyl chloride.

4. It was established that the hydroxyl group in the hydrochlorides of the cholinolytic substances investigated is acetylated much more slowly than that in the free bases and this is evidently connected with the fact that the protonized amino group has no catalytic properties.

5. It was established that the reactivity of quaternary ammonium salts and hydrochlorides is usually practically the same, with the exception of substances in which the hydroxyl is bound to the amino group by a strong intramolecular hydrogen bond. In these cases, the capacity of the hydroxyl group for acetylation in the quaternary salts is much higher than in the hydrochlorides.

6. In a series of cholinolytic substances with similar chemical structures, there is a correspondence between the reactivity of their hydroxyl groups and their cholinolytic activity.

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MOLECULAR ASSOCIATION OF CHOLINOLYTIC SUBSTANCES. I

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The study of the physicochemical properties of physiologically active substances in comparison with the chemical structure and physiological activity may be of substantial help in establishing the mechanism of the action of these substances on an organism and also in the search for new and more active compounds.

Investigations of the infrared absorption spectra of cholinolytic substances which act on an organism like atropine [1, 2] and the rate of their acetylation [3] were published recently.

As a result of these investigations it was established that there is a definite relation between the activity of cholinolytic substances and the state and reactivity of their hydroxyl group. The hypothesis was put forward that one of the factors determining the cholinolytic activity of these substances is their capacity to form intermolecular hydrogen bonds through the hydroxyl.

It seemed profitable to check this by a more direct method. For this purpose, we decided to study the molecular association as this is one of the manifestations of a hydrogen bond. The presence in the substances investigated of nucleophilic nitrogen and oxygen atoms in addition to the hydroxyl group gave grounds for assuming that they have a quite marked capacity to form molecular associates. The degree of association of substances of similar structure should reflect the capacity of their hydroxyl groups to form intermolecular hydrogen bonds. In particular, the formation of an intramolecular hydrogen bond through the hydroxyl should reduce the capacity of the substance for molecular association.

The free bases of ten cholinolytic substances (see table) were investigaged. Their constants and data on their cholinolytic activity were given previously [2]. For comparison, we included substances (I) and (IV), which do not contain a hydroxyl group.

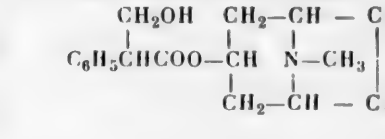
The investigation was carried out by the usual cryoscopic method in benzene solutions with molar concentrations of 0.3 and 0.06. Higher concentrations could not be used because of the low solubility of a series of the substances in benzene and at lower concentrations, the association was not very appreciable. The association factor (the ratio of the number of particles found in solution to the number of particles taken) was calculated from the values obtained for the depression of the freezing point of the solutions. The data obtained are given in the table. In examining them, it should be remembered that a smaller association factor corresponds to a higher degree of association.

As was to be expected, substances (I) and (IV), which do not contain a hydroxyl group, did not show a tendency for molecular association. Three substances containing a hydroxyl (VII, VIII, and IX) did not show a tendency for association either (in any case, within the limits of sensitivity of this method). The hydroxyl group in them has no capacity to form intermolecular hydrogen bonds as it is held in a strong intramolecular hydrogen bond, as was established by infrared spectra [2]. These three substances have comparatively low cholinolytic activity.

If the three remaining diethylamino derivatives (II, V, and VI) are arranged in the order of increasing capacity for molecular association, we obtain the series: (VI) < (II) < (V). It is characteristic that these substances lie in the same sequence with respect to their cholinolytic activity and in the reverse sequence with respect to the degree of binding of their hydroxyls by an intramolecular hydrogen bond [2].

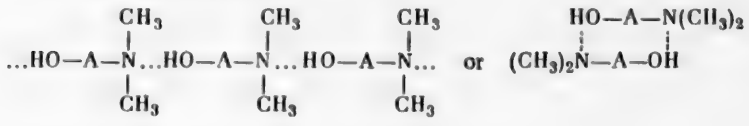
A comparison of substances (II) and (III) shows the strong dependence of the molecular association on the structure of the radicals at the amino group. The latter evidently participates directly in the formation of associates of linear or cyclic types:

Association of Cholinolytic Substances in Benzene

Compound No.	Compound	Association factor	
		0.3 M solution	0.06 M solution
I	$(C_6H_5)_2CHCOOCH_2CH_2N(C_2H_5)_2$	1.0	1.0
II	$(C_6H_5)_2C(OH)COOCH_2CH_2N(C_2H_5)_2$	0.93	0.99
III	$(C_6H_5)_2C(OH)COOCH_2CH_2N(CH_3)_2$	0.69	0.82
IV	$(C_6H_5)_2CHCOSCH_2CH_2N(C_2H_5)_2$	1.0	1.0
V	$(C_6H_5)_2C(OH)COSCH_2CH_2N(C_2H_5)_2$	*	0.83
VI	$(C_6H_5)_2C(OH)CON(CH_3)CH_2CH_2N(C_2H_5)_2$	0.96	1.0
VII	$(C_6H_5)_2C(OH)CH_2OCH_2CH_2N(C_2H_5)_2$	1.0	1.0
VIII	$(C_6H_5)_2C(OH)CH_2SCH_2CH_2N(C_2H_5)_2$	1.0	1.0
IX	$(C_6H_5)_2C(OH)CH_2CH_2N(C_2H_5)_2$	1.0	1.0
X		*	0.70

* This concentration of the substance in benzene could not be reached.

** Atropine as the base.



where A is the chain of atoms connecting the nitrogen and the hydroxyl group.

Finally, we should mention the high tendency for molecular association of atropine, which is one of the most powerful cholinolytic substances.

Thus, if we regard the degree of molecular association of these substances as a measure of the capacity of their hydroxyl groups to form intermolecular hydrogen bonds, it may be considered that the data obtained confirm the hypothesis on the relation between the cholinolytic activity of substances containing a hydroxyl group and the capacity of the latter to form intermolecular hydrogen bonds.

SUMMARY

The molecular association in benzene of a series of cholinolytic substances containing a hydroxyl and a tertiary amino group was investigated cryoscopically.

It was established that the capacity of the substances investigated for molecular association is inversely related to the degree of binding of their hydroxyl by an intramolecular hydrogen bond.

In the series of substances with a diethylamino group investigated there is a correspondence between the capacity for molecular association and cholinolytic activity.

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MOLECULAR ASSOCIATION OF CHOLINOLYTIC SUBSTANCES. II

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For a certain group of cholinolytic substances which contain a hydroxyl in their structure and act on an organism like atropine, it was shown previously that the physiological activity depends on the state and reactivity of their hydroxyl groups [1, 2, 3]. For a smaller group of these compounds, a correspondence was found between the capacity for association in benzene and the cholinolytic activity [4]. The association of the molecules of the substances occurring under these conditions was also determined by the presence and state of the hydroxyl groups. At the same time, it is widely known that cholinolytic activity depends on not only the hydroxyl group, but also on a series of other functional groups present in the molecule of the substance and also on their relative disposition (see, for example, [5-9]). There are many active cholinolytic substances which do not contain a hydroxyl group. However, they all have to contain a group (in particular, an amino group) which is readily ionized in aqueous solution with the conversion of the substance into an organic cation. It can be assumed that the interaction of a cholinolytic substance with the biochemical system of the organism sensitive to acetylcholine (choline receptor) is essentially molecular association or complex formation. Together with the electrostatic attraction between the cationic group of the cholinolytic substance and the anionic group of the receptor (ionic sorption), an essential part must be played by other forces such as hydrogen bonds, van der Waal's forces, and dipole – dipole interaction. The strength of the cholinolytic substance – choline receptor complex will be higher, the greater the number of points at which there is an interaction between them, which, in its turn, depends on the relative disposition of the interacting atoms, i.e., on the chemical structure and geometry of the molecule of the cholinolytic substance.

On this basis it seemed profitable to us to investigate the capacity of cholinolytic substances for molecular association with a series of other organic compounds containing various functional groups.

Since there is every reason to assume that the choline receptor is of a proteinaceous nature, we considered first the groups which are found most often in proteins: COOH, NH_2, NHCO, OH, SH, etc.

As the subject of the investigation we chose three typical atropine-like cholinolytic substances: the diethylaminoethyl ester of diphenylacetic acid (spasmolytin) (I), the dimethylaminoethyl ester of benzilic acid (benzacin) (II), and the diethylaminoethyl ester of benzilic acid (amizyl) (III). All these amines were investigated as the free bases. Their formulas and some of their physicochemical constants are given below.

(I) $(C_6H_5)_2CHCOOCH_2CH_2N(C_2H_5)_2$, b.p. 165° at 1 mm, n^{20}_D 1.5379, d_4^{20} 1.0441.

(II) $(C_6H_5)_2C(OH)COOCH_2CH_2N(CH_3)_2$, b.p. 99.5-101°.

(III) $(C_6H_5)_2C(OH)COOCH_2CH_2N(C_2H_5)_2$, b.p. 54-55°.

As the second component we used phenylacetic acid (IV), phenol (V), benzyl alcohol (VI), n-butanol (VII), n-butylamine (VIII), benzylamine (IX), indole (X), benzyl mercaptan (XI), ethylacetamide (XII), and dimethylformamide (XIII).

For studying the association we used A. N. Izmailov's modification of the cryoscopic method [10-13], which is based on the determination of the deviation from additivity of the cryoscopic depression of the mixture of the two substances, dissolved in an indifferent solvent. We used benzene as the latter.

EXPERIMENTAL

All the substances required for the investigation were purified carefully. The cryoscopic measurements were made in a normal Beckmann apparatus with an electromagnetic stirrer. Two series of cryoscopic measurements were

TABLE 1. Depression in Freezing Point of Solutions of Substances Investigated Δt*

Moles of substance per 1000 g of benzene	Compound											
	I	II	III	IV	V	VI	VIII	IX	X	XI	XII	XIII
0.03	0.160	0.133	0.156	0.083	0.090	0.155	0.160	0.155	0.153	0.154	0.143	0.155
0.05	0.265	0.215	0.260	0.138	0.157	0.260	0.265	0.260	0.257	0.257	0.225	0.257
0.10	0.530	0.407	0.510	0.273	0.300	0.486	0.513	0.516	0.527	0.515	0.385	0.510
0.15	0.800	0.583	0.755	0.408	0.450	0.687	0.760	0.760	0.787	0.770	0.500	0.767
0.20	1.070	0.750	0.990	0.540	0.600	0.870	1.010	0.997	1.030	1.032	0.585	0.997
0.25	1.340	0.910	1.213	0.666	0.740	1.030	1.260	1.216	1.273	1.295		1.215
0.30	1.605	1.065	1.430	0.790	0.875	1.170	1.500	1.435	1.507	1.540		1.425
0.35	1.880		1.637		1.003	1.293	1.745	1.645	1.717			1.627
0.40			1.840		1.130							

* The data for butanol (VII) are not given as they coincided with the data of N. A. Izmailov and A. K. Franke [8].

made to determine the deviation from additivity produced by the interaction of the components. The first series consisted of measurements of the depression in freezing point (Δt) of solutions of the components investigated in benzene at various concentrations (Table 1).

From these data we constructed a graph of the relation of Δt to concentration and calculated the association factor for each substance.

$$f = \frac{\Sigma m_{exp}}{\Sigma m_{anal}}, \text{ where } \Sigma m_{exp} = \frac{\Delta t}{\varepsilon_g}$$

where f is the association factor, Σm_{anal} is the analytical concentration of the substance in moles per 1000 g of benzene; Δt is the depression in the freezing point of the solution; ε_g is the cryoscopic constant of benzene, which equals 5.13.

The second series of measurements consisted of determinations of the depression in freezing point of a series of solutions of mixtures of the two components investigated in various ratios, but with the same total concentration in the solution (in most cases, 0.3 mole per 1000 g of benzene). These solutions were prepared by mixing different proportions of solutions of the separate components with the same concentration. The values found for the depression (Δt_{exp}) are given in Table 2.

We then used the data from the first series of experiments to calculate the depression in freezing point which solutions of the second series would have had had there been no reaction between the components (Δt_{calc}).

$$\Delta t_{calc} = \Delta t_A + \Delta t_B,$$

where Δt_A is the depression which the cholinolytic (A) present in the solution should have given and Δt_B is the depression which the other component (B) should have given.

The difference between Δt_{calc} and Δt_{exp} is the deviation in the property of the system (Δ) caused by the interaction between its components:

$$\Delta = \Delta t_{calc} - \Delta t_{exp}$$

If the components interact to form a compound (complex) than Δ does not equal 0, but is positive.

By plotting the values of Δ corresponding to different ratios of the components on a graph of composition against property, we obtain a curve whose maximum approximately gives the composition of the complex formed A_nB_m, where n and m are the stoichiometric factors.

TABLE 2. Depression in Freezing Point of Systems Investigated in Benzene at Constant Total Concentration Δt_{exp}*

Content of cholinolytic in mixture of two substances (%)	Systems																					
	AI–III	A–I	A–II	A–III	IA–I	IA–II	IA–III	IIA–II	IIIA–I	IIIA–II	IIIA–III	XI–II	X–I	X–II	X–III	IX–II	IIX–II	IIIX–II				
100	1.430	1.605	1.065	1.430	1.610	1.060	1.435	1.065	1.605	1.065	1.430	0.750	1.605	1.065	1.430	1.065	0.750	1.065				
90	1.270	1.490	1.000	1.320	1.560	1.057	1.370	1.067	1.597	1.100	1.400	0.775	1.577	1.108	1.425	1.130	0.760	1.110				
80	1.110	1.345	0.945	1.215	1.503	1.045	1.310	1.073	1.590	1.135	1.353	0.800	1.545	1.153	1.420	1.200	0.765	1.160				
70	0.965	1.205	0.895	1.100	1.440	1.033	1.255	1.077	1.577	1.155	1.315	0.825	1.510	1.196	1.415	1.255	0.770	1.195				
60	0.830	1.185	0.855	1.013	1.387	1.017	1.210	1.083	1.565	1.175	1.297	0.850	1.475	1.240	1.415	1.310	0.760	1.230				
50	0.660	0.990	0.820	0.935	1.340	1.000	1.183	1.087	1.557	1.197	1.295	0.877	1.450	1.287	1.410	1.360	0.755	1.265				
40	0.540	0.905	0.780	0.870	1.000	1.000	1.165	1.095	1.545	1.240	1.313	0.900	1.445	1.335	1.427	1.415	0.740	1.300				
30	0.470	0.850	0.775	0.830	1.265	1.027	1.155	1.100	1.536	1.293	1.340	0.927	1.450	1.380	1.446	1.465	0.710	1.330				
20	0.545	0.835	0.790	0.815	1.233	1.080	1.160	1.105	1.524	1.355	1.390	0.950	1.464	1.427	1.475	1.510	0.665	1.360				
10	0.665	0.840	0.830	0.835	1.195	1.130	1.165	1.110	1.513	1.420	1.420	0.977	1.485	1.470	1.495	1.530	0.623	1.390				
0	0.790	0.870	0.875	0.875	1.170	1.175	1.175	1.120	1.500	1.500	1.500	1.000	1.510	1.510	1.510	1.540	0.585	1.420				

* In all cases the total concentration was 0.3 mole per 1000 g of benzene, with the exception of systems II-IX and II-XII, in which the concentration was 0.2 M.

In cases where interaction occurred between the components and the values of Δ obtained appreciably exceeded the possible experimental error, we calculated the yield of the compound formed from the equation proposed by N. A. Izmailov [13] by the method of sucessive approximations:

$$C_{A_nB_m} = \frac{\Delta\Sigma_{m_i} - C^x_A(f_A - f^x_A) - C^x_B(f_B - f^x_B)}{nf_A + mf_B - 1},$$

where $C_{A_nB_m}$ is the yield of the compound formed in moles per 1000 g of solvent; $\Delta\Sigma_{m_i}$ is the change in the number of particles in the system in moles per 1000 g of solvent, calculated as a fraction by dividing Δ by the cryoscopic constant of benzene (5.13); C^x_A and C^x_B are the concentrations of the interacting components in the equilibrium solution in moles per 1000 g of solvent; f_A and f_B are the association factors in solution without allowance for the interaction between them; f^x_A and f^x_B are the association factors of the interacting components in the equilibrium solution.

If the calculation is carried out correctly, the maximum content of the complex corresponds to the stoichiometric ratio of the components. For this ratio, the yield of the complex was calculated in percents. The corresponding data are given below in Table 3.

From the values found for the complex yields and the concentrations of the monomeric molecules of the starting components in the equilibrium solution ([A] and [B]), we calculated the instability constants of the compounds formed, $K_{inst.}$* which are the equilibrium constants of the association:

$$nA + mB \rightleftarrows A_nB_m$$

$$K_{inst.} = \frac{[A]^n \cdot [B]^m}{[A_nB_m]}$$

The concentrations of the monomeric molecules were calculated from the following formulas:

$$[A] = C^x_A(2f^x_A - 1),$$

$$[B] = C^x_B(2f^x_B - 1)$$

Table 3 gives the values found for the instability constants and their reciprocal logarithms (pK_{inst}). The same table gives the energies of interaction of the components or, more accurately, the normal affinity calculated from the equation

$$A = -RT \ln K_{inst} \text{ (kcal/mole)}.$$

* K_{inst} was calculated for medium concentrations, which give the most reliable data.

TABLE 3. Quantitative Characteristics of the Interaction of the Components in the System Investigated*

Serial No.	System	Complex composition	Complex yield (%)	$K_{inst.}$	$pK_{inst.}$	Energy of formation (kcal/mole)
1	III—IV	AB_2	100			
2	I—V	AB_2	46	$3.0 \cdot 10^{-4}$	3.52	4.48
3	II—V	AB_2	53	$2.3 \cdot 10^{-4}$	3.64	4.63
4	III—V	AB_2	51	$3.5 \cdot 10^{-4}$	3.45	4.39
5	I—VI	AB	26.6	$3.0 \cdot 10^{-1}$	0.52	0.66
6	II—VI	AB_2	43	$7.2 \cdot 10^{-3}$	2.14	2.72
7	III—VI	AB	43	$8.9 \cdot 10^{-2}$	1.05	1.33
8	II—VII	AB	45	$5.8 \cdot 10^{-2}$	1.24	1.58
9	II—VIII	AB	27	$2.2 \cdot 10^{-1}$	0.66	0.84
10	III—VIII	AB	30	$2.7 \cdot 10^{-1}$	0.57	0.72
11	II—IX	AB	15	$3.5 \cdot 10^{-1}$	0.45	0.57
12	I—X	AB	15	$7.8 \cdot 10^{-1}$	0.11	0.14
13	II—X	AB	13	$4.5 \cdot 10^{-1}$	0.35	0.44
14	III—X	AB	17	$7.0 \cdot 10^{-1}$	0.15	0.19
15	II—XIII	AB	13	$4.6 \cdot 10^{-1}$	0.34	0.43
16	II—XII	AB	18	$1.1 \cdot 10^{-1}$	0.95	1.20

* See footnote to table on p.3141.

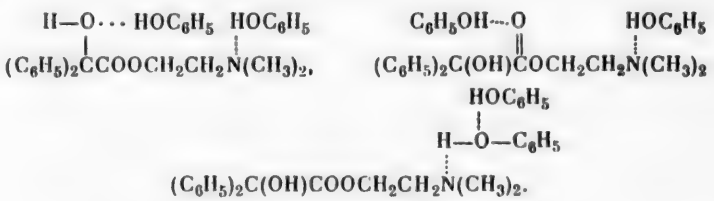
DISCUSSION OF RESULTS

The cholinolytic substances investigated, (I), (II), and (III), contain several functional groups (amino, ester, and hydroxyl groups) which are capable of interacting to some extent with the functional groups of other organic substances investigated, (IV)-(XIII).

The interactions of these substances are different in nature and degree. The strongest interaction occurs in the case of phenylacetic acid. In this case, the reaction product yield at all concentrations of the components equals 100% of theoretical. As a result of this it was impossible to calculate the instability constant and the energy of interaction in this case. The position of the maximum on the curve of Δ against composition corresponds to a compound containing 1 molecule of the cholinolytic substance and 2 molecules of the acid, as is characteristic of other tertiary amines and carboxylic acids [14, 15].

The phenol hydroxyl also showed a high tendency to interact with cholinolytic substances. In all cases of interaction of cholinolytic substance with phenol, the maximum on the composition – property curve lay at 30-40% of the former. On this basis it can be assumed that 2 molecules of phenol interact with 1 molecule of the cholinolytic substance, though, naturally, we cannot exclude the possibility of the formation of other associates with different ratios of the components.

Phenol is known to give strong complexes with many amines [16-18]. Its interaction with carbonyl compounds and alcohols has also been described [16, 19, 20]. In all cases, phenol reacts as a proton donor. It can be assumed, therefore, that in a benzene solution of phenol and a cholinolytic substance, complexes of different composition may be present, for example:



The energy of interaction of cholinolytic substances with phenol, which is close to 4.5 kcal/mole, gives grounds for assuming that here there is actually the formation of quite strong hydrogen bonds.

Alcohols are also known to interact with amines with the formation of a hydrogen bond between the hydroxyl hydrogen and the nitrogen of the amino group [16, 21, 22]. It has also been shown that there is an interaction through

a hydrogen bond between alcohols and the carbonyl groups of ketones and esters [16, 23]. However, the strength of the bond in the case of alcohols is much less than in the case of phenols. In accordance with this, alcohols showed an appreciably lower tendency for association with the cholinolytic substances investigated than phenols. Benzyl alcohol, which has a high proton-donor capacity, reacted much more strongly than n-butanol, as is shown by the composition of the complexes of these alcohols with benacin and their energies of formation.

Amines showed a lower tendency for association with cholinolytic substances investigated than alcohols. Of the two primary amines investigated, only the highly basic n-butylamine reacted sufficiently energetically with the cholinolytic substances. Benzylamine, whose basicity constant is a factor of almost twenty lower than that of butylamine, reacted much more weakly. It is characteristic that butylamine reacted only with the hydroxyl-containing cholinolytic substances (II) and (III). On this basis it can be assumed that butylamine associates through the formation of a hydrogen bond between its nitrogen atom and the hydroxyl group of the cholinolytic substance of the following type:

$$(C_6H_5)_2\overset{\displaystyle O\text{—}H\cdots NH_2C_4H_9}{\overset{|}{C}}COOCH_2CH_2N(CH_3)_2.$$

The nature of the association with cholinolytic substances is evidently completely different in the case of indole. With this substance, an interaction, though it was weak, was observed with all three cholinolytic substances, (I), (II), and (III). The fact that association was also observed with substance (I), which does not contain a hydroxyl, gives grounds for rejecting the above scheme in this case. It is more probable that the indole interacts with a cholinolytic substance like a weak acid with a tertiary amine, the more so as the capacity of indole to give weak complexes with amines has been described in the literature [24].

Although it has been established recently that mercaptans in the liquid state and in solutions can give hydrogen bonds [25], in our experiments, benzyl mercaptan did not show appreciable association with the cholinolytic substances. Weak association with the cholinolytic substances also occurred in the case of the amides, namely, ethylacetamide and dimethylformamide. The former could not be investigated at the required composition because of its low solubility in benzene. Judging by the nature of the relation between Δ and the composition of the mixture, dimethylformamide associates appreciably with the cholinolytic substance (II), but because of the low values of Δ, the quantitative characteristics of the reaction of these two substances are unreliable.

Thus, under the conditions chosen, the cholinolytic substances investigated showed a marked capacity for molecular association with a series of organic compounds containing certain functional groups (COOH, OH, NH_2, etc.). The results obtained confirm the hypothesis that cholinolytic substances of the given type may interact in an organism not only with the anionic group of the choline receptor, but also with some other "anchoring" groups. Among the latter, the most probable is the phenolic hydroxyl of a tyrosine residue, for example. An amino group of the choline receptor may also participate in this interaction. There is also the possibility of amide groups of the protein structure of the choline receptor participating in the interaction with cholinolytic substances.

We consider it our pleasant duty to thank N. A. Izmailov and A. K. Franke for help in applying their method and device.

SUMMARY

1. A crysocopic study was made of the association in benzene of 13 organic substances: the diethylaminoethyl ester of diphenylacetic acid, the dimethyl- and diethylaminoethyl esters of benzilic acid, phenylacetic acid, phenol, benzyl alcohol, n-butanol, n-butylamine, benzylamine, indole, benzyl mercaptan, ethylacetamide, and dimethylformamide.

2. The interaction in benzene solution of the first three of these substances, which are cholinolytics, with the remaining ten organic substances was investigated.

3. It was established that the greatest tendency for interaction with these cholinolytics is shown by phenylacetic acid, then phenol, and to a somewhat lesser extent, benzyl alcohol. Even weaker association with cholinolytics is shown by n-butanol and then n-butylamine and indole, with n-butylamine reacting only with hydroxyl-containing cholinolytics. Even weaker interaction is shown by benzylamine and amides. No interaction with benzyl mercaptan could be detected.

4. Compositions were proposed for the complexes formed and in those case where the reaction between the components was expressed sufficiently strongly, the yield of the interaction product, its instability constant, and its energy of formation were calculated.

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REDUCTION OF NAPHTHOLCARBOXYLIC ACIDS

VII. INDIRECT ELECTROREDUCTION OF 1,4- AND 1,8-NAPHTHOLCARBOXYLIC AND 1- AND 2-NAPHTHOIC ACIDS

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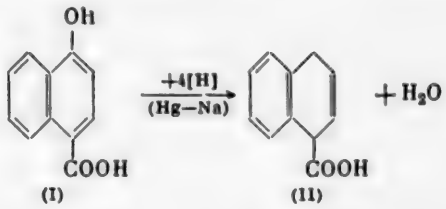
The indirect electroreduction of 1,2-, 2,1-, and 2,3-naphtholcarboxylic acids, which have both functional groups in one nucleus in positions ortho to each other, in our laboratory showed that even such a comparatively small difference in their structure has quite a substantial effect on the nature of the products formed in this reaction [1].

It seemed interesting to determine the effect on the nature of this reaction of a different disposition of the hydroxyl and carboxyl groups in the molecule of the starting naphtholcarboxylic acid. For this purpose we investigated the indirect electroreduction of 1,4- and 1,8-naphtholcarboxylic acids.

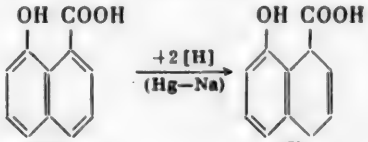
In the reduction of 1,4-naphtholcarboxylic acid (I), which was carried out in an aqueous medium in the presence of p-toluidine by the procedure we described previously [2], the only product which could be isolated from the reaction mixture (59% yield) was 1,4-dihydro-1-naphthoic acid (II).



(I) (II)

A similar partial hydrogenation of the nucleus and elimination of a substituent in the position para to the carboxyl group was observed by Kamm and his co-workers [3] in the reduction of 1,4-ethoxynaphthoic acid with 3% sodium amalgam in the presence of carbon dioxide. No products of reduction at the carboxyl group were observed.

In the reduction of 1,8-naphtholcarboxylic acid (III) under the same conditions, we obtained an almost quantitative yield of 5,8-dihydro-1,8-naphtholcarboxylic acid (IV).



(III) (IV)

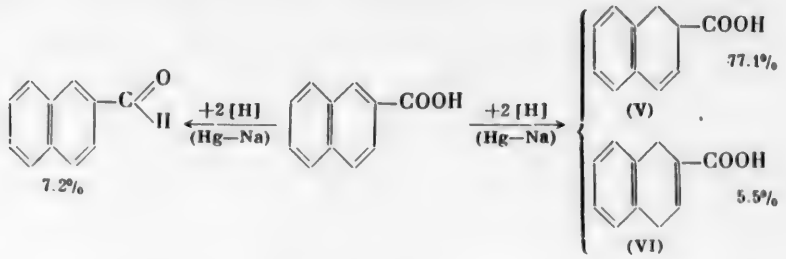
Attention is attracted by the sharp difference in the effects of the hydroxyl and carboxyl groups on the capacity for hydrogenation of the aromatic rings containing them; only the nucleus bearing the carboxyl group is hydrogenated under the conditions examined.

Control experiments showed that neither 1- nor 2-naphthol is reduced either in an aqueous alkali medium or in a solution of methanol containing boric acid. Meanwhile, the reduction of 1- and 2-naphthoic acids by a similar method has been described by a series of authors. It was reported that when the reaction was carried out in an aque-

ous medium in the presence of carbon dioxide, only the corresponding dihydro acids were formed [3, 4]. When the reaction was carried out in the presence of boric acid, only insignificant amounts of the corresponding naphthaldehydes were formed in yields of 1-2% [5].

Our experiments gave more complete data on the reduction of 1- and 2-naphthoic acids under similar conditions. The indirect electroreduction of 1-naphthoic acid gave a 71% yield of 1,4-dihydro-1-naphthoic acid (II), which was identical with that obtained by reduction of 1,4-naphtholcarboxylic acid. It was also possible to detect a very small amount (~ 0.5%) of 1-naphthaldehyde among the reaction products.

In the reduction of 2-naphthoic acid, the corresponding aldehyde was formed to a greater extent (7.2%). The main reaction product here was the dihydro acid. However, in contrast to 1-naphthoic acid, 2-naphthoic acid also added hydrogen at the 1-2 bond and we obtained a mixture of 1,2- and 1,4-dihydro acids, in which 1,2-dihydro-2-naphthoic acids (V) predominated (77.1%), while 1,4-dihydro-2-naphthoic acid (VI) was obtained in only 5.5% yield.



EXPERIMENTAL

Reduction of 1,4-naphtholcarboxylic acid. The 1,4-naphtholcarboxylic acid was obtained in 65-70% yield from o-(4-methoxy-1-naphthoyl)-benzoic acid by fusion with KOH by Schulenburg's method [6]. It had m.p. 189-191° [7].

The reduction was carried out in an electrolyzer [1] in an aqueous medium in the presence of p-toluidine and boric acid and with carbon dioxide passed [2].

A 10 g sample of the acid was dissolved in 300 ml of water, containing 10 g of sodium carbonate. The solution was filtered, 25 g of boric acid and 6.5 g of p-toluidine were added, and the mixture was poured into the electrolyzer. A current of 5 amp was passed for 2.5 hr. The mixture was stirred for a further 0.5 hr, the precipitate of p-toluidine and boric acid separated, and the filtrate made weakly acid with 10% H_2SO_4 and treated several times with ether. The ether extracts were washed 5-6 times with 50 ml portions of saturated sodium bicarbonate solution. The bicarbonate solution was acidified and left overnight in a refrigerator. The precipitated oil crystallized. Recrystallization from ligroin gave colorless needles of 1,4-dihydro-1-naphthoic acid (II) with m.p. 88-89°. The yield was 5.45 g (59%). According to literature data [4] the m.p. is 91°.

Found %: C 75.97, 76.16; H 5.83, 5.96. $C_{11}H_{10}O_2$. Calculated %: C 75.84; H 5.79.

Reduction of 1,8-naphtholcarboxylic acid. The 1,8-naphtholcarboxylic acid was obtained from technical naphthostyryl [8]. It had m.p. 168-169° (from water) [8].

The reduction and isolation of the products were as in the case of 1,4-naphtholcarboxylic acid. Acidification of the bicarbonate solution liberated an oil, which crystallized after a day. The crystals were collected. The yield of 5,8-dihydro-1,8-naphtholcarboxylic acid (IV) was 8.4 g. Extraction of the acid filtrate with ether yielded a further 1.1 g of the substance, which was identical with the main reaction products. The m.p. was 150-151° (from toluene). An aqueous solution of the substance gave a yellow-green color with $FeCl_3$ and coupled with the diazo compound obtained from p-toluidine.

Found %: C 69.96, 69.83; H 5.61, 5.43; OH 8.8, 8.9. Acid number 295.2. $C_{11}H_{10}O_3$. Calculated %: C 69.46; H 5.30; OH 8.9. Acid number 295.0.

The reduction of 1- and 2-naphthols was carried out in an aqueous alkaline medium and in methanol containing boric acid. The reaction product was extracted with ether after acidification. The ether extracts were treated repeatedly with 5% KOH solution, washed with water, and dried. Evaporation of the ether left 0.1-0.3 g of a dark oil, which

did not form a hydrazone with 2,4-dinitrophenylhydrazine. Acidification of the alkaline extracts yielded a substance which was identical with the starting naphthol.

Reduction of 1-naphthoic acid. The 1-naphthoic acid was obtained by oxidation of 1-acetylnaphthalene [9]. It had m.p. 158-160° (decomp. from toluene).

The reduction was analogous to that of 1,4-naphtholcarboxylic acid. The reaction mixture was filtered. The precipitate was mixed with 100 ml of 30% H_2SO_4 and steam distilled. To the distillate obtained was added a saturated solution of 2,4-dinitrophenylhydrazine in 5% hydrochloric acid. The red precipitate (~0.1 g) was collected, dried, and recrystallized from glacial acetic acid. It had m.p. 253-254° (decomp.). The 2,4-dinitrophenylhydrazone of 1-naphthaldehyde has m.p. 254° (decomp.) [10]. The yield of 1-naphthaldehyde was 0.5%, calculated on the 2,4-dinitrophenylhydrazone.

Fractional precipitation yielded 7.1 g of a substance from the filtrate. Recrystallization of this from ligroin gave colorless needles with m.p. 88-89°. The substance did not depress the melting point of the 1,4-dihydro-1-naphthoic acid obtained by reduction of 1,4-naphtholcarboxylic acid.

The yield of 1,4-dihydro-1-naphthoic acid was 70.2%.

Reduction of 2-naphthoic acid. 2-Naphthoic acid was obtained by oxidation of 2-acetylnaphthalene [11]. It had m.p. 184-186° (decomp. from benzene).

The reduction was analogous to that of 1,4-naphtholcarboxylic acid and the reaction product was treated as in the experiment with 1-naphthoic acid.

Steam distillation yielded 0.65 g (72%) of 2-naphthaldehyde with m.p. 60-61°, which corresponds to literature data [12].

Found %: C 84.70, 84.91; H 5.21, 5.23. $C_{11}H_8O$. Calculated %: C 84.59; H 5.16.

Acidification of the filtrate to pH ~5 with 10% H_2SO_4 yielded 0.55 g (5.5%) of 1,4-dihydro-2-naphthoic acid (VI). After recrystallization from ligroin, the substance had m.p. 160-161°, which corresponds to literature data [3].

Found %: C 76.16, 76.53; H 5.71, 5.82. $C_{11}H_{10}O_2$. Calculated %: C 75.84; H 5.79.

Further acidification of the filtrate to pH ~1 yielded 1,2-dihydro-2-naphthoic acid (V) with m.p. 100-101° (from ligroin) [3]. The yield was 7.8 g (77.1%).

Found %: C 76.20, 76.26; H 5.83, 5.78. $C_{11}H_{10}O_2$. Calculated %: C 75.84; H 5.79.

SUMMARY

1. The indirect electroreduction of 1,4- and 1,8-naphtholcarboxylic acids, 1- and 2-naphthols, and 1- and 2-naphthoic acids was carried out in an aqueous medium in the presence of boric acid.

2. It was shown that the disposition of the functional groups in 1,4-naphtholcarboxylic acid in positions para to each other leads to hydrogenation of the nucleus with the elimination of the hydroxyl group. The yield of 1,4-dihydro-1-naphthoic acid was 59%.

3. 1,8-Naphtholcarboxylic acid is hydrogenated in the nucleus containing the carboxyl group to give an almost quantitative yield of 5,8-dihydro-1,8-naphtholcarboxylic acid.

4. 1-Naphthoic acid is reduced to 1,4-dihydro-1-naphthoic acid (71%). 1-Naphthaldehyde is formed in insignificant amounts (0.5%).

5. 2-Naphthoic acid is converted into 2-naphthaldehyde (7.2%), 1,4-dihydro-2-naphthoic acid (5.5%), and 1,2-dihydro-2-naphthoic acid (77.1%).

6. It was shown that 1- and 2-naphthols are not reduced either in an aqueous alkaline medium or in methanol.

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SYNTHESIS OF DI(METHYLINDENYL)IRON

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Original article submitted December 24, 1960

The hydrocarbons cyclopentadiene, indene and fluorene include the same structural element, namely a cyclopentadienyl ring and are characterized by a tendency for chemical conversions caused by the lability of the hydrogen atoms in the methylene group of the five-membered ring, but these proceed with different intensities.

An interesting characteristic of these hydrocarbons is their power to form stable organometallic compounds with transition metals, in particular, iron, in which the cyclopentadienyl ring shows aromatic properties. A great amount of work has been devoted to the synthesis and investigation of the physical and chemical properties of dicyclopentadienyliron, which is called ferrocene [1].

Of the two possible analogs of ferrocene (based on indene and fluorene), only one, namely, diindenyliron has been prepared [2-4].

The purpose of the present investigation was the synthesis and study of some properties of the closest homolog of diindenyliron, namely, di(methylindenyl)iron. 1-Methylindene was obtained by a method described in the literature from indanone-1, which was synthesized by cyclization of hydrocinnamoyl chloride. Di(methylindenyl)iron was obtained by three methods: by condensation of the organomagnesium and lithium compounds prepared from methylindene with $FeCl_2$ and by the "amine" method [5], i.e., by direct synthesis from methylindene and $FeCl_2$ in the presence of diethylamine.

Investigation showed that like diindenyliron [2], di(methylindenyl)iron is unstable in organic solvents in the presence of air, especially in benzene and n-hexane.

It was found to be more stable in ether at a temperature close to zero. It was under precisely these conditions that we were able to isolate di(methylindenyl)iron from a concentrated ether solution of it. The dry di(methylindenyl)-iron was quite stable in air, as was also observed in the case of diindenyliron [2].

Di(methylindenyl)iron is a solid black crystalline substance with m.p. 107-109°. The elementary composition and molecular weight found corresponded to the calculated values.

EXPERIMENTAL

Hydrocinnamic acid (m.p. 47.7°) was obtained in 85-90% yield by electrolytic reduction of cinnamic acid [6, 7].

Hydrocinnamoyl chloride was obtained in 90% yield by the procedure in [8] and had the following constants:

B.p. 89° at 3 mm, d_4^{20} 0.9970, $n^{20}D$ 1.5930, MR_D 46.64; calc. 46.74. Literature data [9]: b.p. 105° at 10 mm.

Indanone-1 was prepared by the procedure in [10, 11]. We obtained 193.8 g (90%) of the substance with m.p. 41°. 1-Methylindene was synthesized by the procedure in [11]. We obtained 99 g (80%) of the substance with b.p. 135° at 11 mm and $n^{20}D$ 1.5657, which correspond to literature data [11].

Synthesis of di(methylindenyl)iron. a) Reaction of 1-methylindenylmagnesium bromide with ferrous chloride. The ferrous chloride required for the condensation was obtained by reduction of ferric chloride with chlorobenzene [12].

To 0.25 mole of ethylmagnesium bromide, which was prepared in di-n-butyl ether at 110-115°, was added a solution of 0.25 mole of 1-methylindene in 50 ml of di-n-butyl ether at room temperature. This operation was accompanied by a spontaneous rise in the temperature of the reaction mixture from 18 to 27° and a sharp change in its color, namely, from gray to brown. With the subsequent addition of 0.12 mole of $FeCl_2$ to the reaction mixture in

portions, there was a slight rise in temperature. The contents of the flask were then heated at 110-120° for 5 hr, when the color changed to black.

The di-n-butyl ether was distilled from the reaction products, finally at 120° and 3 mm. The residue was treated with ether. The ether extracts were evaporated to a small volume and cooled to –5° to yield a small amount of a black substance, which had m.p. 107-108° after recrystallization from ether (–20°).

b) Reaction of 1-methylindenyllithium with ferrous chloride. To the n-butyllithium prepared by the procedure in [13] from 0.5 g-at. of lithium, 0.2 mole of n-C_4H_9Br, and 150 ml of ether was added a solution of 0.19 mole of 1-methylindene in 50 ml of ether. On heating on a water bath for 4 hr, the mixture acquired a cherry red color. When 0.095 mole of $FeCl_2$ was added to the reaction mixture cooled to 16°, the temperature rose to 25°. The reaction mixture was then heated on a water bath for 3 hr. The ether solution of the reaction product was filtered, evaporated to a small volume, and cooled to –5°. After 12 hr it had deposited a solid black substance; 1/4 of it was washed with water, 10% HCl, again with water, and then cold ether (–20°) and dissolved in boiling ether. When cooled to –50°, the ether solution deposited 3.5 g (23%) of a black substance. The product was purified by sublimation. It sublimed at 70° and 3 mm and had m.p. 107-109°.

Found %: C 76.96; H 6.13. M 302 (by Rast's method). $C_{20}H_{19}Fe$. Calculated %: C 76.43; H 5.73. M 314.

Extraction of the remaining part of the crude reaction product with benzene and n-heptane did not give positive results.

c) Reaction of 1-methylindene with ferrous chloride in the presence of diethylamine. To a solution of 0.046 mole of 1-methylindene in 40 ml of diethylamine was added 0.023 mole of $FeCl_2$ with vigorous stirring. The temperature of the reaction mixture rose from 18 to 41° and its color changed sharply (to black). After the reaction mixture had been stirred for 18 hr, the unreacted 1-methylindene and diethylamine were removed by distillation with steam heated to 120°.

The residue was dried in a vacuum desiccator and sublimed. A small amount of material was obtained. The sublimation temperature was 70° at 3 mm and the m.p. 107-108°.

Found M 294 (by Rast's method). $C_{20}H_{19}Fe$. Calculated M 314.

SUMMARY

The first homolog of diindenyliron, di(methylindenyl)iron was synthesized by three different methods, namely, through organomagnesium and lithium derivatives of 1-methylindene and from 1-methylindene and $FeCl_2$ in diethylamine solution, and some of its properties were studied.

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C-ACYLATION OF HETEROCYCLIC KETO ENOLS

VI. CYCLIZATION OF PHENYLHYDRAZONES OF 3-ACYL-4-HYDROXYCOUMARINES

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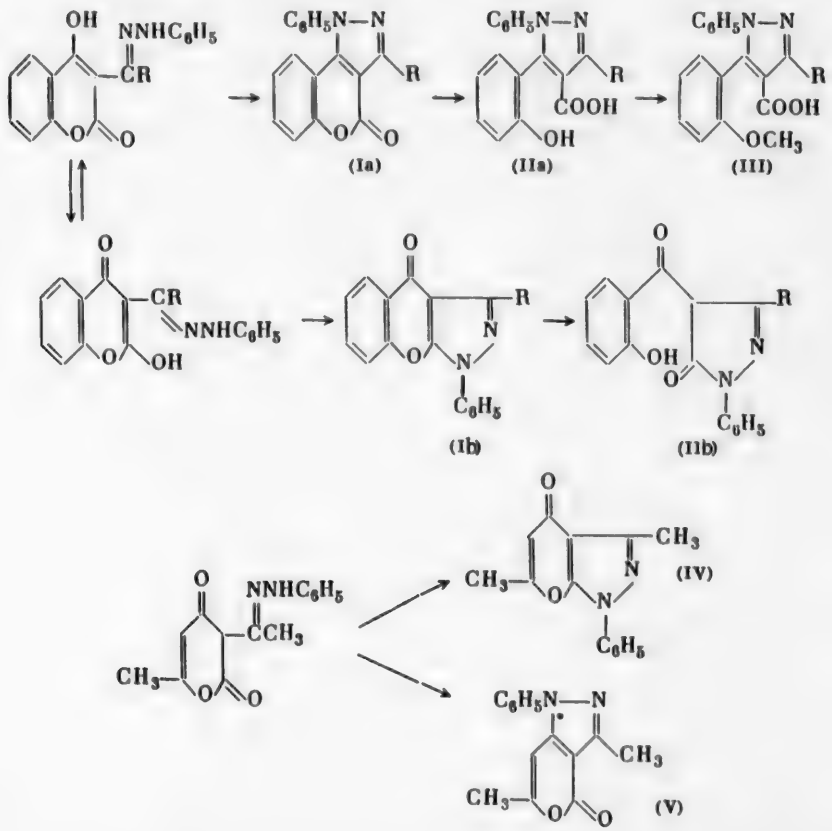
The presence of tautomerism of the coumarin – chromone type in the series of 4-hydroxycoumarin and its 3-halo and hydroxy derivatives was first reported in 1951 [1, 2]. Tautomerism of this type was subsequently observed also with 3-alkyl(aryl)-4-hydroxycoumarins [3], methylene-3,3'-bis(4-hydroxycoumarin) [4], and carbethoxymethylene-3,3'-bis(4-hydroxycoumarin) [5]. There is no information in the literature on the capacity of 3-acyl-4-hydroxycoumarins to react in the form of the corresponding 2-hydroxychromones.

We decided to extend the cyclization of phenylhydrazones of β-keto enols to derivatives of 3-acyl-4-hydroxycoumarin and establish the structure of the products of this reaction. In this case, one might have expected the formation of a derivative of pyrazolocoumarin (Ia) or pyrazolochromone (Ib). It is noteworthy that structure (IV) was proposed for the cyclization product of the phenylhydrazone of dehydracetic acid [6], but it was soon shown that in actual fact, the structure of this product corresponds to (V) [7].



By dehydration of 3-acyl-4-hydroxycoumarin phenylhydrazones, we obtained a series of compounds (see table) with very similar ultraviolet spectra, indicating that they had similar structures (Fig. 1).

To establish the structures of these substances, we subjected the simplest of the compounds we synthesized (I), in which R = CH_3, to alkaline hydrolysis. Had the substance obtained had structure (Ia), it would have been converted into 1-phenyl-5-(o-hydroxyphenyl)-3-methylpyrazole-4-carboxylic acid (IIa), while a substance with structure (Ib) apparently would yield 1-phenyl-4-(o-hydroxybenzoyl)-3-methylpyrazolone-5 (IIb) or its degradation products. The ultraviolet spectrum of the hydrolysis product we obtained was found to be similar to the absorption spectrum of 1,5-diphenyl-3-methylpyrazole-4-carboxylic acid [8] and it differed considerably from the corresponding spectrum of 1-phenyl-3-methyl-4-benzoylpyrazolone-5 [9] (Fig. 2). This gave grounds for assuming that the hydrolysis product had structure (IIa). In analogy with the preparation of 1,5-diphenyl-3-methylpyrazole-4-carboxylic acid [8], starting from 0-methoxybenzoylacetoacetic ester and phenylhydrazine, we synthesized 1-phenyl-5-(o-methoxyphenyl)-3-methylpyrazole-4-carboxylic acid, which was found to be identical with compound (III), obtained by methylation of the hydrolysis product. This was confirmed by the data of ultraviolet (Fig. 3) and infrared spectra (Fig. 4).

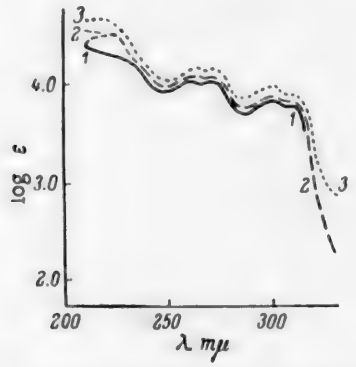


Fig. 1. Ultraviolet spectra of alcohol solutions of the cyclization products (I) of 3-acyl-4-hydroxycoumarin phenylhydrazones (table). 1) R = CH_3; 2) R = = C_2H_5; 3= R = n-C_4H_9.

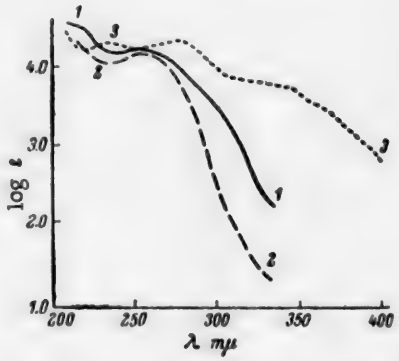


Fig. 2. Ultraviolet spectra of alcohol solutions. 1) Compound (II, R = CH_3); 2) 1,5-diphenyl-3-methylpyrazole-4-carboxylic acid; 3) 1-phenyl-3-methyl-4-benzoylpyrazolone-5.

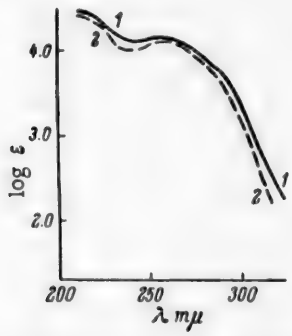


Fig. 3. Ultraviolet spectra of solutions. 1) Substance obtained by methylation of compound (II); 2) 1-phenyl-5-(o-methoxyphenyl)-3-methylpyrazole-4-carboxylic acid.

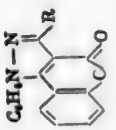
Thus, it was established that 3-acyl-4-hydroxycoumarin phenylhydrazones are cyclized to form pyrazolocoumarin derivatives.

EXPERIMENTAL

5-Phenyl-3-alkylpyrazolo-(4,5-c)-coumarins. The phenylhydrazone of the 3-acyl-4-hydroxycoumarin [10] was boiled for 50 min with a small amount of p-toluenesulfonic acid in anhydrous xylene with distillation of the water. The cooled solution was filtered to remove the tarry residue and ligroin added to the filtrate to precipitate the corresponding pyrazolocoumarin, which was purified by recrystallization from alcohol. The results of the experiments are given in the table.

1-Phenyl-5-(o-hydroxyphenyl)-3-methylpyrazole-4-carboxylic acid (IIa). A 10 g sample of compound (Ia, R = CH_3) was added to a solution of 1.7 g of Na in 110 ml of methanol, the mixture stirred until the precipitate dissolved completely, 150 ml of water added to the solution, and the mixture boiled for 20 min. The cooled solution

Pyrazolocoumarins



R	Yield (%)	M. p.	Form of crystals	Found (%)			Empirical formula	Calculated (%)		
				C	H	N		C	H	N
CH_3	82	226—227°	Needles	73.88, 73.91	4.30, 4.39	10.12, 10.09	$C_{17}H_{12}O_2N_2$	73.90	4.37	10.14
C_2H_5	57	163.5—164	Prisms	74.71, 74.89	4.96, 4.98	9.74, 9.69	$C_{18}H_{14}O_2N_2$	74.46	4.86	9.65
n-C_4H_9	42	119.5—120	Needles	—	—	9.10, 8.95	$C_{20}H_{18}O_2N_2$	—	—	8.80
iso-C_4H_9	50	165.5—166	Prisms	—	—	8.86, 8.77	$C_{20}H_{18}O_2N_2$	—	—	8.80
n-C_5H_{11}	73	103—104	Prisms	—	—	8.48, 8.37	$C_{21}H_{20}O_2N_2$	—	—	8.42

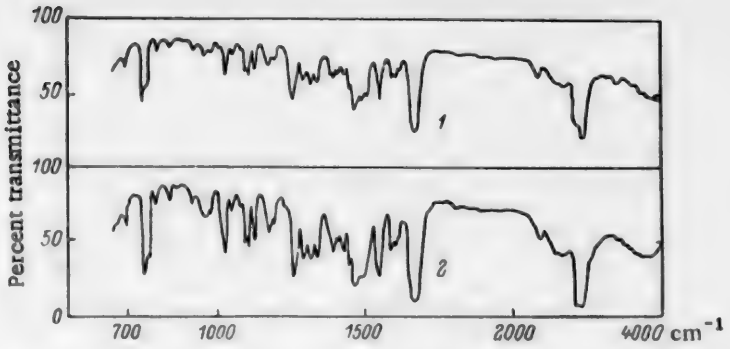


Fig. 4. Infrared spectra. 1) Substance obtained by methylation of compound (II); 2) 1-phenyl-5-(o-methoxyphenyl)-3-methyl-pyrazole-4-carboxylic acid.

was poured into iced water, the precipitate collected and dissolved in 80 ml of 10% of NaOH, and the alkaline solution acidified with 10% hydrochloric acid with cooling. The colorless precipitate was collected, washed with water, and dried. The yield was 9.8 g (92%). The colorless platelets had m.p. 217-217.5° (from aqueous methanol).

Found %: C 69.45, 69.59; H 4.78, 4.98; N 9.63, 9.67. $C_{17}H_{14}O_3N_2$. Calculated %: C 69.37; H 4.57; N 9.51.

o-Methoxybenzoylacetoacetic ester. To a suspension of Na-acetoacetic ester (from 4.3 g of acetoacetic ester and 0.9 g of sodium) in 70 ml of anhydrous benzene was added a solution of 8.8 g of o-methoxybenzoyl chloride [11] in 30 ml of anhydrous benzene dropwise. The mixture was boiled and stirred for 8 hr, cooled, and poured onto ice and the nonaqueous layer separated, washed with 5% bicarbonate solution and water, and dried with sodium sulfate. Vacuum distillation yielded 6.8 g (50%) of o-methoxybenzoylacetoacetic ester. The thick, slightly yellowish liquid had b.p. 174° (6 mm) and n^{20}_D 1.5530.

Found %: C 63.64, 63.79; H 6.40, 6.46. $C_{14}H_{16}O_5$. Calculated %: C 63.62; H 6.10.

1-Phenyl-5-(o-methoxyphenyl)-3-methylpyrazole-4-carboxylic acid. a) A mixture of 3.8 g of 1-phenyl-5-(o-hydroxyphenyl)-3-methylpyrazole-4-carboxylic acid, 100 ml of 10% sodium carbonate solution, and 5 ml of dimethyl sulfate was boiled for 5 hr. The cooled solution was filtered and acidified with 10% hydrochloric acid and the precipitate collected, washed with water, and dried. The yield of methoxy product was 3.2 g (80%). The colorless, rhombic crystals had m.p. 215.5-217° (from methanol).

Found %: C 69.79, 69.81; H 5.23, 5.20; N 8.92, 8.95. $C_{18}H_{16}O_3N_2$. Calculated %: C 70.11; H 5.23; N 9.08.

b) To 4.4 g of o-methoxybenzoylacetoacetic ester was gradually added 1.8 g of phenylhydrazine, the mixture kept at room temperature for 30 min and then boiled for 2 hr with 5 g of potassium hydroxide in 10 ml of methanol and diluted with 50 ml of water. The methanol was removed by distillation, the residue extracted with ether, the aqueous layer acidified with 10% sulfuric acid with cooling, and the colorless precipitate collected, washed with water, and dried. Recrystallization

from methanol gave colorless rhombic crystals. The weight was 2.2 g (43%, calculated on the starting o-methoxybenzoylacetoacetic ester) and the m.p. 215-216°. A mixed melting point with the substance obtained by method "a" was not depressed.

SUMMARY

It was established that in the dehydration of phenylhydrazones of 3-acyl-4-hydroxycoumarins, cyclization occurs at position 4 to give the corresponding derivatives of pyrazolo-(4,5-c)-coumarin.

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RATIO OF ISOMERIC AZOXY COMPOUNDS FORMED BY OXIDATION OF o,o'-DISUBSTITUTED AZO COMPOUNDS

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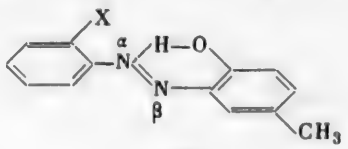
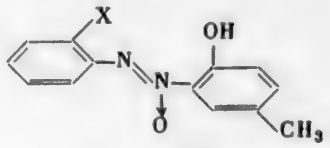
The oxidation of 2-hydroxy-5-methylazobenzene (Ia) with hydrogen peroxide in glacial acetic acid forms almost exclusively the corresponding β-azoxy compound (IIa) [1]. Oxidation of the corresponding O-acetylated azo compound yields largely the α-isomer (IIf), which gives on hydrolysis 2-hydroxy-5-methyl-α-azoxybenzene (IIIa).



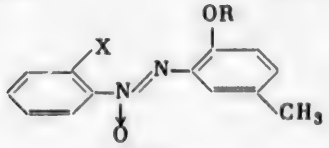
(I)

a) X = H,
b) X = OCH$_3$,
c) X = CH$_3$,
d) X = Br,
e) X = NO$_2$.



(II)

a) X = H,
b) X = OCH$_3$,
c) X = CH$_3$,
d) X = Br,
e) X = NO$_2$.

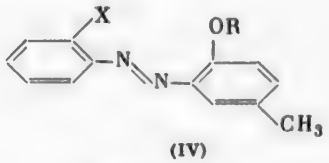


(III)

a) X = H,
b) X = OCH$_3$,
c) X = CH$_3$,
d) X = Br,
e) X = NO$_2$,
} R = H

f) R = COCH$_3$, X = H.

In an attempt to apply this method to o,o'-disubstituted azo compounds (Ib-e), in all cases we obtained only the β-isomers of the corresponding azoxy compounds instead of the expected α-isomers.



(IV)

Nature of R

X	COCH$_3$	COC$_6$H$_5$	SO$_3$C$_6$H$_4$CH$_3$—4′	SO$_3$C$_6$H$_3$(NO$_2$)$_2$—2′,4′
OCH$_3$	a	e	i	—
CH$_3$	b	f	j	m
Br	c	g	k	n
NO$_2$	d	h	l	—

In the light of general concepts [2-7] on the mechanism of this type of reaction with the participation of organic peracids as electrophilic reagents, it can be assumed that the main factors determining the formation of isomers

of the azoxy compounds are the nature of the electron density distribution at the nitrogen atoms of the azo group and the steric hindrance to the approach to the cyclic form of the peracid molecule to these nitrogen atoms. From this point of view, the formation of the α-isomer of (IIIf) may be explained by the fact that acetylation of the ortho-hydroxyl group increases the negative induction effect and thus reduces the electron density at the β-nitrogen atom and hampers the formation of the β-isomer.

On the other hand, we cannot exclude the possibility that the screening of the α-nitrogen atom, which has quite a strong hydrogen bond in the unacylated compound (Ia) [8, 9], has a positive effect on the preferential formation of the β-isomer (IIa) in the oxidation of compound (Ia).

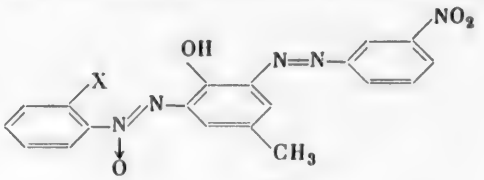
The formation of the β-isomer in the oxidation of compound (IVb), i.e., even when the ortho-position relative to the α-nitrogen atom bears an electron-donor methyl group, which produces an increase in the electron density at this nitrogen atom, may be produced both by the effect of conjugation of this group with the β-nitrogen atom and by partial shielding of the α-nitrogen atom from the approach of the peracid molecule.

A similar situation occurs in the case of the ortho-methoxy derivative (IVa) where the -I effect of the methoxyl group produces a decrease in electron density at the α-nitrogen atom (Table 1).

These considerations compelled us to increase the electron-acceptor properties of the acyloxy group by replacing acetyl by such acyl groups as benzoyl, p-toluenesulfonyl, and even 2,4-dinitrobenzenesulfonyl.

Despite the fact that with an increase in the electron-acceptor properties of the acyloxy group the reaction rate fell appreciably as a result of a decrease in the electron density at the azo group, even in the case of the O-benzoyl derivatives (IVe and f), which contain electron-donor groups in the ortho-position, there was the formation of small amounts of α-isomers (Table 1). Even better results were obtained in the case of O-(p-toluenesulfonyl) derivatives (IVi-k).

However, the introduction of a 2,4-dinitrobenzenesulfonyl group led to strong hindrance to oxidation in general and this was evidently produced by the exceptionally high electrophilicity of this group. Only in the oxidation of compounds (IVm) and (IVn) was it possible (after hydrolysis) to detect the corresponding α-isomers of the azoxy compounds and identify them in the form of coupling products with p-nitrodiazobenzene (Vb, c).



a) X = OCH_3,
b) X = CH_3,
c) X = Br,
d) X = NO_2.

(V)

It was reported previously [1], that the α-isomer (IIIa), in contrast to the β-isomer (IIa), is capable of coupling with diazobenzene. We found that this reaction on paper is not sufficiently characteristic. Much better results are obtained with p-nitrodiazobenzene: the reaction proceeds rapidly and the azoxyazo dyes (V, a-d) formed with the α-isomers show solvatochromism, making this reaction selective. Solutions of compounds (Va-d) in aqueous alkali are violet and in alcohol, acetone, and dimethylformamide in the presence of alkalis, deep blue. The effect of the nature of the solvents in producing a bathochromic shift in the series ethanol < acetone < dimethylformamide is similar to that observed [10] for some azo compounds.

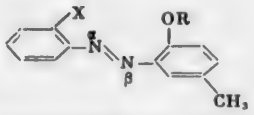
This reaction was found to be suitable for chromatographic identification of isomeric azoxy compounds and was used successfully for converting small amounts of the α-isomers which were difficult to isolate into the corresponding azoazoxy compounds (Va-d).

EXPERIMENTAL*

2-Hydroxy-2'-methoxy-5-methylazobenzene (Ib), 2-hydroxy-2',5-dimethylazobenzene (Ic), 2'-bromo-2-hydroxy-5-methylazobenzene (Id), and 2'-nitro-2-hydroxy-5-methylazobenzene (Ie). The compounds were synthesized by diazotization of o-anisidine, o-toluidine, o-bromoaniline, and o-nitroaniline, respectively, and coupling with p-cresol in a soda-alcohol medium.

* The melting points and analyses of the new compounds obtained in the present work are given in Table 2.

TABLE 1. Ratio of Isomeric α- and β-Azoxy Compounds Formed by Oxidation of Azo Compounds (IV) with Hydrogen Peroxide in Glacial Acetic Acid



X \ R	H yield (%)		$COCH_3$ yield (%)		COC_6H_5 yield (%)		$SO_2C_6H_4CH_3$-4' yield (%)	
	α	β	α	β	α	β	α	β
OCH_3	—	29.6	—	23.5	+	15.9	32.5	—
CH_3	—	33.3	—	25.0	+	17.09	3.8	8.4
Br	—	15.0	—	10.2	—	6.7	0.11	15.5
NO_2	—	30.7	—	27.0	—	7.3	±	1.08

Footnote: — not detected, ± traces detected, + small amounts detected.

Compounds (Ib-d) were purified by recrystallization from methanol and compound (Ie) by reprecipitation with ligroin from chloroform solution. The constants of the compounds obtained corresponded to literature data [11-14].

2'-Methoxy-2-acetoxy-5-methylazobenzene (IVa), 2'-acetoxy-2,5'-dimethylazobenzene (IVb), 2'-bromo-2-acetoxy-5-methylazobenzene (IVc), and 2'-nitro-2-acetoxy-5-methylazobenzene (IVd). To a solution of 4.0 g of the appropriate compound (IB-d) in 100 ml of acetic anhydride was added 4 g of anhydrous sodium acetate and the solution boiled for 18 hr [in the case of product (IVa) 6 hr] and, after cooling, poured into 300 ml of 70% aqueous methanol. The precipitated products were collected and recrystallized from methanol (≈ 100 ml) and product (IVc) was recrystallized from 50% methanol.

The yield of compound (IVa) was 1.27 g (27%). The orange powder was readily soluble in organic solvents and sparingly soluble in water.

The yield of compound (IVb) was 3.5 g (70%). The yellow-brown powder was readily soluble in alcohols and sparingly soluble in water.

The yield of compound (IVc) was 3.3 g (80%). It had m.p. 85-86°, which corresponds to literature data [13].

The yield of compound (IVd) was 3.8 g (90%). It had m.p. 100-101°, which corresponds to literature data [15].

2'-Methoxy-2-benzoyloxy-5-methylazobenzene (IVe), 2'-benzoyloxy-2,5'-dimethylazobenzene (IVf), 2'-bromo-2-benzoyloxy-5-methylazobenzene (IVg), and 2'-nitro-2-benzoyloxy-5-methylazobenzene (IVh). To a solution of 4.0 g of the appropriate compound (Ib-e) in 160 ml of 20% NaOH were added 8 ml of pyridine and 25 ml of benzoyl chloride, the mixture shaken for 1 hr, and the precipitate collected, washed with dilute (1 : 10) sulfuric acid (~100 ml), water (~100 ml), 5-6% sodium carbonate solution (~50 ml), and water (~50 ml), and recrystallized from methanol (150 ml) [500 ml of compound (IVe)]. The yield of compound (IVe) was 3.42 g (60%), of compound (IVf) 3.5 g (60%), of compound (IVg) 3.7 g (68.5%) (m.p. 107-108°, which corresponds to literature data [13]), and of compound (IVh) 4.0 g (74.0%). The products (IVe-h) were orange powders, which were soluble in acetone, ethanol, and methanol.

2'-Methoxy-2-(p-toluenesulfonyloxy)-5-methylazobenzene) (IVi), 2'-(p-toluenesulfonyloxy)-2,5'-dimethylazobenzene (IVj), 2'-bromo-2-(p-toluenesulfonyloxy)-5-methylazobenzene (IVk), and 2'-nitro-2-(p-toluenesulfonyloxy)-5-methylazobenzene (IVl). To a solution of 4.0 g of the appropriate compound (Ib-e) in 100 ml of acetone was added 7 ml of 20% of NaOH and then 6 g of p-toluenesulfonyl chloride was introduced in portions with stirring over a period of 10-15 min. The mixture was stirred for 1 hr at room temperature and for 2-3 hr with heating under reflux and then half of the acetone was removed by distillation. The product liberated was collected and recrystallized from methanol (~150 ml). In the case of compound (IVl), the reaction mixture was poured onto ice (~100 g) after removal of the acetone.

TABLE 2. Melting Points and Analyses of New Compounds

Compound No.	M. p.	Empirical formula	Analysis results (%)					
			C		H		N	
			found	calculated	found	calculated	found	calculated
II b	117—117.5°	$C_{14}H_{14}O_3N_2$	65.51, 65.31	65.14	5.33, 5.68	5.42	11.01, 11.11	10.85
II c	86—86.5	$C_{14}H_{14}O_2N_2$	69.31, 69.36	69.42	5.28, 5.24	5.78	11.56, 11.56	11.57
III b	69	$C_{14}H_{14}O_3N_2$	64.93, 64.90	65.14	4.86, 5.04	5.42	10.52, 10.77	10.85
IV a	49	$C_{16}H_{16}O_3N_2$	67.43, 67.33	67.60	5.94, 6.14	5.60	—	—
IV b	68—69	$C_{16}H_{16}O_2N_2$	71.80, 71.96	71.60	6.30, 6.10	5.90	—	—
IV e	150—151	$C_{21}H_{18}O_3N_2$	73.09, 73.21	72.83	5.52, 5.43	5.20	8.37, 8.51	8.09
IV f	113—113.5	$C_{21}H_{18}O_2N_2$	76.67, 76.63	76.36	5.78, 5.91	5.45	8.64, 8.66	8.48
IV h	140	$C_{20}H_{15}O_4N_3$	—	—	—	—	11.46, 11.35	11.63
IV i	133—134	$C_{21}H_{20}O_4N_2S$	—	—	—	—	7.07, 6.91	7.07
IV j	109—110	$C_{21}H_{20}O_3N_2S$	—	—	—	—	7.23, 6.93	7.36
IV k	102—103	$C_{20}H_{17}O_3N_2SBr$	—	—	—	—	6.08, 5.97	6.26
IV l	104—104.5	$C_{20}H_{17}O_5N_3S$	—	—	—	—	10.03, 10.08	10.2
IV m	178.5	$C_{20}H_{16}O_7N_4S$	—	—	—	—	11.8, 11.7	12.28
IV n	166	$C_{10}H_{13}O_7N_4SBr$	—	—	—	—	10.41, 10.64	10.75
V b	187—188.5	$C_{20}H_{17}O_4N_5$	—	—	—	—	17.80, 18.00	17.90
V c	197—198	$C_{19}H_{14}O_4N_5Br$	—	—	—	—	15.13	15.35

The yield of compound (IVi) was 4.0 g (61.5%), of compound (IVj) 3.72 g (55.5%), of compound (IVk) 3.5 g (57.3%), and of compound (IVl) 2.0 g (32.7%). Compounds (IVi-l) were orange powders, which were readily soluble in ethanol and methanol, and sparingly soluble in water.

2'-(2",4"-Dinitrobenzenesulfonyloxy)-2,5'-dimethylazobenzene (IVm) and 2'-bromo-2-(2",4"-dinitrobenzenesulfonyloxy)-5-methylazobenzene (IVn). With stirring and cooling to −5°, to a solution of 5.5 g of 2,4-dinitrobenzenesulfonyl chloride [16] in toluene (30 ml) was gradually added a solution of 4.0 g of compound (Ic) or compound (Id) in toluene (30 ml) to which had first been added a solution of 0.5-0.4 g of sodium in 15 ml of methanol. When the whole of the solution had been added, the reaction mixture was stirred for 1 hr. After the solution had been filtered, the product was precipitated with ligroin (b.p. 40-60°, ~100 ml), washed with ligroin (~30 ml), and purified by precipitation with ligroin from toluene solution. The yield of compound (IVm) was 2.0 g (25.0%) and of compound (IVn) 2.0 g (28.1%). Compounds (IVm and n) were orange powders, which were readily soluble in xylene and toluene and sparingly soluble in alcohols and ligroin.

Reaction of α-isomers of ortho-hydroxyazoxy compounds with p-nitrodiazobenzene. Onto filter paper were successsively deposited 0.05-0.10 ml portions of a solution of the substance investigated in acetone or formamide and a solution of p-nitrobenzenediazonium chloride and then 0.1-0.2 ml of 10% sodium hydroxide solution. A blue or blue-black color appeared in the case of α-isomers of the ortho-hydroxyazoxy compounds (IIa-e). In this way it was possible to detect ~1-2 mg of an α-isomer. The corresponding β-isomers do not give this reaction; ortho-hydroxyazo compounds in high concentrations give only a weak color.

Oxidation of 2-hydroxy-2'-methoxy-5-methylazobenzene (Ib), 2'-hydroxy-2,5'-dimethylazobenzene (Ic), 2'-bromo-2-hydroxy-5-methylazobenzene (Id), and 2'-nitro-2-hydroxy-5-methylazobenzene (Ie). To a solution of 1.2 g of compound (Ib), 1.1 g of compound (Ic), 1.4 g of compound (Id), or 1.2 g of compound (Ie) in 100 ml of glacial acetic acid was added 16.7 ml of 30% hydrogen peroxide and the mixture heated for 18 hr at 75-80°. The color of the solution gradually changed from dark red to orange. After filtration, the solution was poured onto 200 g of ice. The precipitated product was washed on a filter with distilled water until the filtrate was no longer acid to Congo, dried on the filter in the dark, and recrystallized from a mixture of 25 ml of dioxane and 0.5 ml of water in the case of compounds (Ib and c), 40 ml of a mixture of acetone and water (3 : 1) in the case of (Id), and 80 ml of 80% methanol in the case of compound (Ie).

Compound (Ib) yielded 0.37 g (29.6%) of 2-(2'-methoxyphenylazoxy)-4-methylphenol (IIb). The yellow scales were readily soluble in methanol, ethanol, chloroform, benzene, ether, dioxane, and other organic solvents and sparingly soluble in water.

Compound (Ic) yielded 0.40 g (33.3%) of 2-(2'-methylphenylazoxy)-4-methylphenol (IIc). The yellow powder was readily soluble in organic solvents and sparingly soluble in water.

Compound (Id) yielded 0.20 g (15%) of 2-(2'-bromophenylazoxy)-4-methylphenol (IId). It had m.p. 96° [17].

Compound (Ie) yielded 0.40 g (30.7%) of 2-(2'-nitrophenylazoxy)-4-methylphenol (IIe). It had m.p. 102-103° [17].

No other products were isolated from the oxidation. Qualitative reactions for the α-isomers of the ortho-hydroxyazoxy compounds on the filtrates were negative.

Oxidation and subsequent hydrolysis of 2'-methoxy-2-acetoxy-5-methylazobenzene (IVa), 2'-acetoxy-2,5'-dimethylazobenzene (IVb). 2'-bromo-2-acetoxy-5-methylazobenzene (IVc), and 2'-nitro-2-acetoxy-5-methylazobenzene (IVd). To a solution of 1.39 g of compound (IVa), 1.3 g of compound (IVb), 1.6 g of compound (IVc), or 1.44 g of compound (IVd) in 100 ml of glacial acetic acid was added 16.7 ml of 30% hydrogen peroxide and the mixture heated for 18 hr at 75-80°. After isolation (see above) the product was dissolved in 100 ml of acetone, 2 g of KOH added, the mixture boiled for 4 hr, and then the solution cooled, filtered, acidified to Congo with concentrated hydrochloric acid with cooling in ice, and poured on to ~200 g of ice. The precipitated product was recrystallized from a mixture of dioxane and water in the case of compounds (IVa and b), from aqueous acetone in the case of compound (IVc), and from aqueous methanol in the case of compound (IVd) (see above).

Compound (IVa) yielded 0.3 g (23.5%) of compound (IIb) with m.p. 117-117.5°. It was identified by a mixed melting point.

Compound (IVb) yielded 0.3 g (25%) of product (IIc) with m.p. 86-86.5°. It was identified by a mixed melting point.

Compound (IVc) yielded 0.15 g (10.2%) of compound (IId) with m.p. 96°. It was identified by a mixed melting point.

Compound (IVd) yielded 0.35 g (27.0%) of compound (IIe) with m.p. 103-104°. It was identified by a mixed melting point.

No other products were isolated from the oxidation. Qualitative reactions for the α-isomers of the ortho-hydroxyazoxy compounds on the filtrates were negative.

Oxidation and subsequent hydrolysis of 2'-methoxy-2-benzoyloxy-5-methylazobenzene (IVe), 2'-benzoyloxy-2,5'-dimethylazobenzene (IVf), 2'-bromo-2-benzoyloxy-5-methylazobenzene (IVg), and 2'-nitro-2-benzoyloxy-5-methylazobenzene (IVh). To a solution of 1.7 g of compound (IVe), 1.6 g of compound (IVf), 1.9 g of compound (IVg), or 1.8 g of compound (IVh) in 100 ml of glacial acetic acid was added 16.7 ml of 30% hydrogen peroxide and the mixture heated at 75-80° for 30 hr in the case of compounds (IVe and f) and for 72 hr in the case of compounds (IVg and h). The oxidation product isolated was dissolved in a mixture of 50 ml of acetone, 50 ml of water, and 50 ml of methanol, 2 g of KOH added, and the mixture boiled under reflux for 12 hr. After the reaction mixture had been cooled and filtered, it was made acid to Congo with concentrated hydrochloric acid with cooling in ice and poured onto 200 g of ice. The product liberated was recrystallized from a mixture of dioxane and water in the case of compounds (IVf and e), from aqueous acetone in the case of compound (IVg), and from aqueous methanol in the case of compound (IVh) (see above).

Compound (IVe) yielded 0.2 g (15.9%) of compound (IIb) with m.p. 117-117.5°. As in the cases below, the product was identified by a mixed melting point. The water-dioxane filtrate from the recrystallization of compound (IIb) gave a clear qualitative reaction for the o-hydroxy-α-azoxy compound.

Compound (IVf) yielded 0.2 g (17.09%) of compound (IIc) with m.p. 86-86.5°. The filtrate from recrystallization of compound (IIc) gave a clear qualitative reaction for the o-hydroxy-α-azoxy compound.

Compound (IVg) gave 0.1 g (6.7%) of the product (IId) with m.p. 95.5-96°.

Compound (IVh) gave 0.1 g (7.3%) of compound (IIe) with m.p. 102-102.5°.

In the case of products (IVg and h), the test for the o-hydroxy-α-azoxy compound on the filtrate was negative.

Oxidation of 2'-methoxy-2-(p-toluenesulfonyloxy)-5-methylazobenzene (IVi). To a solution of 1.94 g of compound (IVi) in 150 ml of glacial acetic acid was added 16.7 ml of 30% of hydrogen peroxide and the mixture heated for 24 hr at 75-80°. The oxidation product isolated (as above) was dissolved in a mixture of 100 ml of acetone, 100 ml of water, and 100 ml of methanol, 4 g of KOH added, and the mixture boiled for 18 hr. The solution was then

cooled, filtered, acidified to Congo with concentrated hydrochloric acid with cooling with ice, diluted with ~200 ml of water, and extracted with chloroform (2 · 50 ml). The chloroform extract was purified with charcoal, the chloroform evaporated, and alcohol (20-30 ml) added to the residue. The precipitate was collected and recrystallized twice from a mixture of 20 ml of alcohol and 0.5 ml of water and once from a mixture of 15 ml of methanol and 0.5 ml of water.

We obtained 0.41 g (32.5%) of 2-(2'-hydroxy-5'-methylphenylazoxy)-anisole (IIIb). The yellow powder was readily soluble in organic solvents and aqueous alcohol solutions and sparingly soluble in water. It gave a positive reaction [18] for an azoxy group and a clear reaction for an o-hydroxy-α-azoxy compound.

Compound (IIIb) had R_f 0.70 and compound (IIb) R_f 0.19 (solvent – 60% ethanol, ascending chromatography, paper – "slow for chromatography").

The half-wave potential* of compound (IIIb) was 0.91 v and of compound (IIb) 0.78 v.

No other products were isolated from the oxidation.

Oxidation of 2'-methyl-2'-(p-toluenesulfonyloxy)-5-methylazobenzene (IVj). To a solution of 3.72 g of compound (IVj) in 200 ml of glacial acetic acid was added 33.4 ml of 30% hydrogen peroxide and the mixture heated at 75-80° for 24 hr. It was then cooled to room temperature, a further 25 ml of 30% hydrogen peroxide added, and heating continued for a further 6 hr at 75-80°. The oxidation product was isolated as described above for the unacylated compounds. The oxidation product was hydrolyzed analogously to the methoxyl derivative (see above). The solution after hydrolysis was cooled, filtered, and poured onto a mixture of ~200 g of ice and ~50 ml of hydrochloric acid. The precipitate was collected on a layer of charcoal and the filtrate extracted with 50 ml of chloroform (extract A). The precipitate with the charcoal was heated with ~50 ml of 2 M sodium hydroxide solution and the solution filtered and acidified to Congo with hydrochloric acid. The precipitate was collected and the filtrate extracted with ~50 ml of chloroform (extract B). The precipitate was recrystallized from 130 ml of 80% methanol.

We obtained 0.2 g (8.4%) of a substance with m.p. 85°, which was found to be identical (mixed melting point) with the product (IIc) obtained from compound (Ic). A qualitative reaction [18] for an azoxy group was positive and that for an o-hydroxy-α-hydroxyazoxy compound was negative.

The chloroform extracts (A and B) and the filtrate from recrystallization of (IIc) gave a clear positive reaction for an o-hydroxy-α-hydroxyazoxy compound. They were combined and evaporated to 1/3 of the volume and 20 ml of alcohol, 80 ml of 10% of NaOH, and 5 g of sodium carbonate were added. To this solution was added a solution of p-nitrobenzenediazonium chloride (from 0.3 g of p-nitroaniline in 20 ml of 18% hydrochloric acid) with cooling. After 2-3 hr, the precipitated product was collected, mixed with dilute (1 : 1) hydrochloric acid (70 ml), collected by filtration, washed with water (~50 ml), dissolved in a mixture of 45 ml of alcohol and 10 ml of 10% of NaOH, precipitated with hydrochloric acid (~30 ml), and recrystallized from a mixture of acetic acid (25 ml) and water (0.5 ml). The recrystallized product was washed with hot ligroin (b.p. 40-60°, 25-30 ml).

We obtained 0.15 g (3.8%) of 2-[(4"-nitrobenzene)-(1"-azo-1')-2'-hydroxy-5'-methylphenylazoxy]-toluene (Vb). The black needles were readily solulble in chloroform, benzene, methanol, and ethanol, and sparingly soluble in ligroin and water. An aqueous alkaline solution was violet, while a solution in alcohol, acetone, or formamide was blue.

Oxidation of 2'-bromo-2-(p-toluenesulfonyloxy)-5-methylazobenzene (IVk). To a solution of 6.6 g of compound (IVk) in glacial acetic acid (300 ml) was added 75 ml of 30% hydrogen peroxide and the mixture heated at 75-80° for 90 hr with 20 ml portions of 30% hydrogen peroxide added after every 30 hr after the solution had been cooled. The product isolated after oxidation was dissolved in a mixture of 100 ml of acetone, 100 ml of water, and 100 ml of methanol, 4 g of KOH added, and the mixture boiled for 30 hr. The cooled and filtered solution was poured onto a mixture of ~200 g of ice and ~50 ml of hydrochloric acid. The precipitate was collected and the filtrate diluted with 100 ml of water and extracted with chloroform (50 ml). The precipitate was crystallized fractionally from 70 ml of 70% acetone.

From the third fraction we obtained 0.7 g (15.5%) of a substance with m.p. 96°, which was found to be identical with compound (IId) obtained from compound (Id).

From the first and second fractions we isolated products (1.3 g) m.p. 103-104°. This was evidently a mixture of compound (IId) and the starting compound (Id).

* The polarographic measurements were made by Yu. I. Vainshtein and M. D. Shirokova.

The filtrate from recrystallization of the product (IId) and the chloroform extract gave a clear positive reaction for an o-hydroxy-α-azoxy compound. The product (IIId) was isolated as a dye with p-nitrobenzenediazonium chloride (Vc) analogously to product (Vb) (see above). Compound (Vc) was purified by acidification of an alkaline-alcohol solution (45 ml of alcohol and 10 ml of 10% NaOH) and crystallized fractionally from 60 ml of 70% of acetic acid. From the 3rd fraction we obtained 0.0075 g (0.11%) of 2-[(4"-nitrobenzene)-(1"-azo-1)-2'-hydroxy-5'-methylphenyl-azoxy]-bromobenzene (Vc). The dark brown powder was readily soluble in organic solvents and sparingly soluble in water. An aqueous alkaline solution was violet, while a solution in alcohol, acetone, or formamide was blue.

From the 1st and 2nd fractions we isolated 0.05 g of a less pure product with m.p. 189-190°.

Oxidation of 2'-nitro-2-(p-toluenesulfonyloxy)-5-methylazobenzene (IVl). To a solution of 3 g of compound (IVl) in glacial acetic acid (150 ml) was added 30 ml of 30% hydrogen peroxide and the mixture heated at 75-80° for 108 hr with 20 ml portions of 30% hydrogen peroxide added after every 36 hr with cooling. After hydrolysis of the oxidation products, it was possible to isolate 0.02 g (1.08%) of compound (IIe). It had m.p. 102-103°. It was identified by its melting point. The filtrate gave a weak reaction for an o-hydroxy-α-azoxy compound.

Oxidation of 2'-(2',4'-dinitrobenzenesulfonyloxy)-2,5'-dimethylazobenzene (IVm) and 2'-bromo-2-(2',4"-dinitrobenzenesulfonyloxy)-5-methylazobenzene (IVn). To a suspension of 1.0 g of compound (IVm) or 1.27 g of compound (IVn) in glacial acetic acid (150 ml) was added 15 ml of 30% hydrogen peroxide and the mixture heated at 75-80° for 90 hr with 5 ml portions of 30% hydrogen peroxide added after every 30 hr. After the mixture had been cooled, the precipitate was removed by filtration and the filtrate poured onto ~100 g of ice. We obtained the starting compounds in yields of 60% and 62.9% respectively.

The filtrate were treated analogously to the oxidation products of (IVj and k) (see above). We isolated traces of compound (Vb) and (Vc).

SUMMARY

An investigation was made of the effect of acylation of the hydroxyl groups of ortho-substituted ortho-hydroxy-azo compounds on the yield of isomeric azoxy compounds and conditions were found for increasing the yield of the α-isomer of the ortho-hydroxyazoxy compounds.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

2-METHYLOXAZOLO-(5,4-g)-BENZTHIAZOLE AND DYES FROM IT

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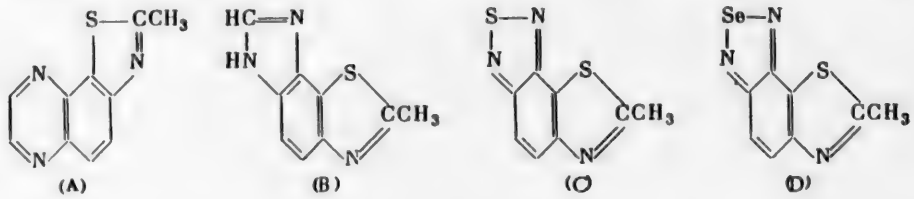
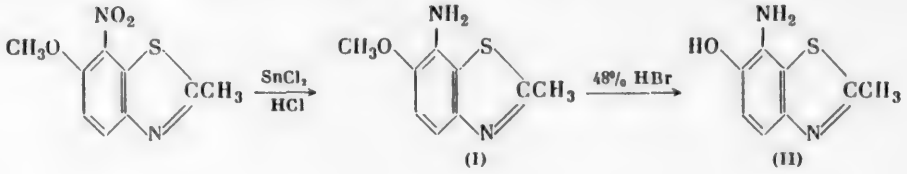
In previous work, descriptions were given of the syntheses of heterocycles consisting of a benzthiazole nucleus condensed with pyrazine (A) [1], imidazole (B) [2], thiadiazole (C) [3], and selenodiazole (D) [3] nuclei.



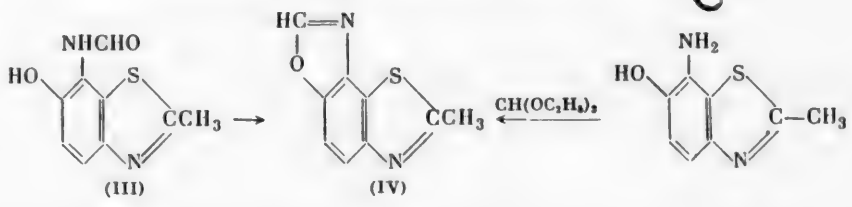
The purpose of the present work has the synthesis of 2-methylbenzthiazole condensed with an oxazole nucleus, namely, 2-methyloxazolo-(5,4-g)-benzthiazole (IV) and the preparation of cyanine dyes from it.

2-Methyloxazolo-(5,4-g)-benzthiazole was synthesized in the following way: nitration of 2-methyl-6-methoxybenzthiazole yielded 2-methyl-6-methoxy-7-nitrobenzthiazole with m.p. 151°, which has been described in the literature [4]. The authors demonstrated strictly that the nitro group occupies position 7 of the benzthiazole nucleus. Reduction of the 7-nitro derivative yielded 2-methyl-6-methoxy-7-aminobenzthiazole (I), which was demethylated to yield 2-methyl-6-hydroxy-7-aminobenzthiazole with m.p. 194° (II).



The latter was converted into 2-methyloxazolo-(5,4-g)-benzthiazole by two methods.

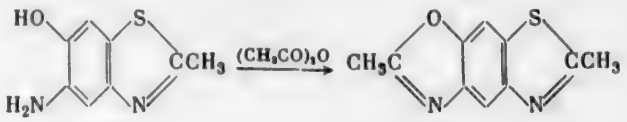
Boiling with formic acid formed 2-methyl-6-hydroxy-7-formylaminobenzthiazole (III). Vacuum distillation of the formyl derivative led to the formation of a product, which, after purification, had m.p. 140° and corresponded in analysis to the expected 2-methyloxazolo-(5,4-g)-benzthiazole (IV).



2-Methyl-6-hydroxy-7-aminobenzthiazole was boiled with a large excess of orthoformic ester and, after removal of the latter by distillation and appropriate purification, an excellent yield of the product with m.p. 140° was obtained and this did not depress the melting point of the previous product (IV).

The structure of the 2-methyloxazolo-(5,4-g)-benzthiazole obtained by this method is undoubtedly correct.

No oxazolobenzthiazoles have been described in the literature with the exception of 2,6-dimethyloxazolo-(4,5-f)-benzthiazole, which was described in an American patent [5]. Reduction of the product from coupling 2-methyl-6-hydroxybenzthiazole with benzenediazonium chloride yielded a compound with m.p. 193°, to which the author assigned the structure of 2-methyl-5-amino-6-hydroxybenzthiazole (E). Condensation of the latter with acetic anhydride and subsequent vacuum distillation yielded a substance with m.p. 270°, which, in the opinion of the author, was 2,6-dimethyloxazolo-(4,5-f)-benzthiazole (F).



(E) (F)

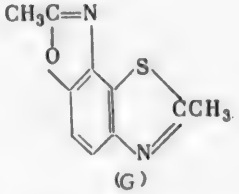
Literature data show that 2-methyl-6-substituted benzthiazoles react with electrophilic reagents to form largely 7-substituted derivatives, while 5-substituted derivatives are obtained in very low yield. Thus, the nitration of 2-methyl-6-acetylaminobenzthiazole formed exclusively 2-methyl-6-acetylamino-7-nitrobenzthiazole [6]. The nitration of 2-methyl-6-chlorobenzthiazole yields largely the 7-nitro derivative and only a very small amount of the 5-substituted derivative [7]. Analogously, 2-methyl-6-methoxybenzthiazole forms mainly the 7-nitro derivative on nitration [4].

It was to be expected therefore that on introduction of a phenylazo group into the benzthiazole nucleus, the main reaction product would be the 7- and not the 5-azo compound.

We repeated this synthesis and obtained a product which did not depress the melting point of the 2-methyl-6-hydroxy-7-aminobenzthiazole (II) which we obtained. We then condensed this product with orthoformic ester and isolated an oxazolobenzthiazole derivative with m.p. 140°, which did not depress the melting point of the 2-methyloxazolo-(5,4-g)-benzthiazole (IV) which we obtained.

Thus, it is evident that in the reaction of benzenediazonium chloride with 2-methyl-6-hydroxybenzthiazole, the phenylazo group enters position 7 of the benzthiazole nucleus. The 2,6-dimethyloxazolo-(4,5-f)-benzthiazole described in the patent actually has the structure of 2,7-dimethyloxazolo-(5,4-g)-benzthiazole (G).

2-Methyloxazolo-(5,4-g)-benzthiazole (IV) was converted into the iodoethylate, from which dyes were obtained in the usual way (see table).

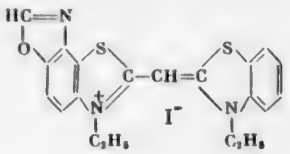
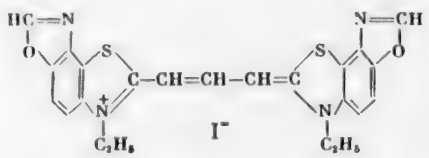
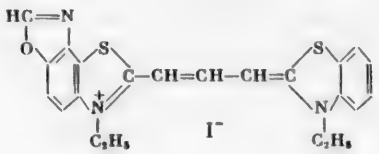
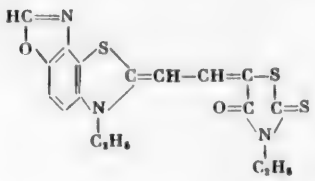
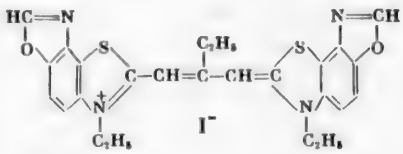
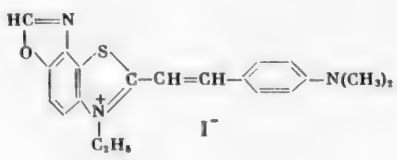


(G)

The data in the table show that the addition of an oxazole ring to the benzthiazole nucleus produces an insignificant displacement of the absorption maximum toward long wavelengths in the corresponding cyanine dyes. A comparison of the absorption maximum of the unsymmetrical carbocyanine (VII) with the absorption maximum of the symmetric N,N'-diethylcarbocyanine indicates the absence of deviations. From this it follows that the basicity of oxozolo-(5,4-g)-benzthiazole differs little from benzthiazole. The introduction of an ethyl group into the meso-position of the symmetrical carbocyanine did not affect the absorption maximum.

EXPERIMENTAL

2-Methyl-6-Methoxybenzthiazole. Into a 1 liter iron vessel were placed 200 g of potassium hydroxide and 200 ml of water. The solution was heated to 125-130° and to it was added 57.6 g of 2-amino-6-methoxybenzthiazole [8] with m.p. 161°. Foaming with the liberation of ammonia began at 135-140°, the temperature rose to 160°, and the reaction mixture was kept at this temperature until the liberation of ammonia ceased (75-90 min from the beginning of the reaction). Then 500 ml of water was added carefully to the mixture, the darkly colored solution filtered, and the filtrate neutralized to Congo with concentrated hydrochloric acid with external cooling in ice. The

Substance No.	Structure of dye	Yield (in %)	M. p.
(V)		30	294—295°
(VI)		63	292—293
(VII)		53	285—286
(VIII)		22	299—300 (decompn.)
(IX)		26	284
(X)		62	265—266

light gray precipitate of 1-mercapto-2-amino-5-methoxybenzene was collected, washed with water, and pressed out well. To this precipitate were added 50 ml of benzene and 50 ml of acetic anhydride and the mixture boiled for 3 hr. To the cooled reaction mixture was added 100 ml of water and 40% sodium hydroxide solution to a strongly alkaline reaction, the benzene layer separated, and the aqueous layer extracted twice with 25 ml portions of benzene. The solvent was distilled from the benzene solution and the remaining 2-methyl-6-methoxybenzthiazole vacuum distilled at 133-135° and 6 mm. The yield was 30 g (58%). Literature data: b.p. 170° at 20 mm and 176° at 25 mm [9].

The picrate was obtained by mixing alcohol solutions of the components and was recrystallized from alcohol. The light yellow needles had m.p. 174°.

Found %: N 13.51, 13.59; S 7.63, 7.80. $C_9H_9ONS \cdot C_6H_3O_7N_3$. Calculated %: N 13.72; S 7.84.

2-Methyl-6-methoxy-7-nitrobenzthiazole was obtained by nitration of 2-methyl-6-methoxybenzthiazole under the conditions given in the literature [4]. The yield was 74% and the m.p. 151-152°.

Absorption maximum (in mμ)	Emprical formula	% I		% S	
		found	calcu-lated	found	calcu-lated
425	$C_{20}H_{18}ON_3S_2I$	25.09, 25.03	25.04	—	—
564	$C_{23}H_{19}ON_4S_2I$	22.35, 22.25	22.12	—	—
562	$C_{22}H_{20}ON_3S_2I$	23.20, 23.18	22.96	12.17, 12.20	12.00
526	$C_{17}H_{15}ON_3S_3$	—	—	24.43, 24.35	24.67
564	$C_{25}H_{13}O_2N_4S_2I$	20.69, 20.63	21.06	10.67, 10.79	10.62
536	$C_{20}H_{20}ON_3SI$	26.73, 26.54	26.62	N 8.75, 8.86	N 8.80

2-Methyl-6-methoxy-7-aminobenzthiazole (I). A 20 g sample of 2-methyl-6-methoxy-7-nitrobenzthiazole was suspended in 100 ml of concentrated hydrochloric acid and to this suspension was added a solution of 85 g of stannous chloride in 85 ml of concentrated hydrochloric acid in one portion. The temperature of the mixture rose and a clear colorless solution was formed. After 2 hr, the precipitate of the binary tin salt was collected, washed with concentrated hydrochloric acid, and dissolved in 200 ml of water with heating. The solution was filtered, cooled to 10°, and made strongly alkaline with 40% sodium hydroxide solution. The pink precipitate was collected, washed twice with small amounts of iced water, and recrystallized from 2 liters of water with charcoal. We obtained 9.7 g (56%) of colorless needles with m.p. 121-122°.

Found %: N 14.62, 14.69. $C_9H_{10}ON_2S$. Calculated %: N 14.43.

2-Methyl-6-hydroxy-7-aminobenzthiazole (II). A 23.9 g sample of 2-methyl-6-methoxy-7-aminobenzthiazole was boiled with 200 ml of 48% hydrobromic acid under reflux for 6 hr. On cooling, the solution deposited coarse crystals of 2-methyl-6-hydroxy-7-aminobenzthiazole hydrobromide, which were collected, pressed out well, and

washed with ether. The weight was 31.9 g (99%). The hydrobromide was recrystallized from alcohol and ether for analysis. The fine colorless needles had m.p. 275°.

Found %: Br 30.60, 30.67. $C_8H_8ON_2S \cdot HBr$. Calculated %: Br 30.65.

To a hot solution of 32 g of the hydrobromide in 300 ml of water was added a hot solution of 40 g of sodium acetate in 50 ml of water. The colorless crystalline precipitate of 2-methyl-6-hydroxy-7-aminobenzthiazole was collected, washed with water, and recrystallized from water with charcoal. The weight was 17.8 g (82%) and the m.p. 194°.

Found %: N 15.66, 15.50; S 17.88, 17.94. $C_8H_8ON_2S$. Calculated %: N 15.55; S 17.77.

2-Methyl-6-hydroxy-7-formylaminobenzthiazole (III). A solution of 4 g of 2-methyl-6-hydroxy-7-aminobenzthiazole in 30 ml of 85% formic acid boiled for 3 hr. The solution was diluted with 10 ml of water, treated with charcoal, and neutralized with ammonia. The precipitate was collected, washed with water and recrystallized from water. The yield was 2.2 g (48%) and the m.p. 219°.

Found %: N 13.47, 13.25; S 15.40, 15.60. $C_9H_8O_2N_2S$. Calculated %: N 13.45; S 15.38.

2-Methyloxazolo-(5,4-g)-benzthiazole (IV). a) From formyl derivative (III). A 4 g sample of 2-methyl-6-hydroxy-7-aminobenzthiazole was boiled with formic acid for 3 hr, the formic acid removed in a water-pump vacuum, and the dry residue distilled at 160-164° and 5 mm. The yield was 2.1 g (58%) and the m.p. 125-127°. The distillate obtained was triturated with a 5% solution of sodium hydroxide to remove traces of the starting material, washed with water, and recrystallized from water. After two recrystallizations, it had m.p. 140°.

Found %: N 14.49, 14.41; S 16.95, 17.00. $C_8H_5ON_2S$. Calculated %: N 14.73; S 16.84.

b) A mixture of 20 g of 2-methyl-6-hydroxy-7-aminobenzthiazole and 150 ml of orthoformic ester was boiled under reflux for 3 hr, the excess orthoformic ester removed in a water-pump vacuum, and the solid residue triturated with 5% alkali solution, washed with water, and dried. The yield was 18 g (86%) and the melting point of the crude product was 136-137°. Recrystallization from aqueous methanol yielded 17.3 g (82%) of colorless needles with m.p. 140°, which did not depress the melting point of the previous preparation.

2-Methyloxazolo-(5,4-g)-benzthiazole is readily soluble in alcohol and hot water, sparingly soluble in cold water, and insoluble in ether and ligroin.

The iodoethylate of 2-methyloxazolo-(5,4-g)-benzthiazole was obtained by heating 5 g of the base with 10 g of ethyl iodide in a sealed tube at 100° for 5 hr. The iodoethylate was recrystallized from methanol to yield 3.6 g (40%) of lustrous yellow scales with m.p. 260-261° (decomp.).

Found %: I 36.50, 36.62. $C_{11}H_{11}ON_2SI$. Calculated %: I 36.70.

The monomethynecyanine (V) was obtained by heating 0.17 g of the iodoethylate of 2-methyloxazolo-(5,4-g)-benzthiazole and 0.17 g of the iodoethylate of 2-methylmercaptobenzthiazole in 5 ml of anhydrous alcohol in the presence of 0.5 g of triethylamine on a water bath for 30 min. The dye was recrystallized from methanol. It formed light yellow needles.

The symmetrical carbocyanine (VI) was obtained by boiling 0.79 g of the iodomethylate with 0.6 g of orthoformic ester in 2 ml of pyridine for 1 hr. The dye was recrystallized twice from alcohol. It formed fine violet needles.

The unsymmetrical carbocyanine (VII) was obtained by heating 0.35 g of the iodoethylate of 2-methyloxazolo-(5,4-g)-benzthiazole and 0.45 g of the iodoethylate of the acetanilidovinyl derivative of 2-methylbenzthiazole and 3 drops of triethylamine in 2 ml of acetic anhydride. The product was purified by recrystallization from ethanol. It formed violet needles with a metallic luster.

The merocyanine (VIII) was obtained by boiling 0.35 g of the iodoethylate and 0.3 g of N-ethylacetaniliodomethylenerhodanine in 25 ml of alcohol with 0.5 g of triethylamine for 10 min. The dye was purified by washing with water, alcohol, and ether. It formed fine dark red needles.

The meso-substituted carbocyanine (IX) was obtained by heating 0.87 g of the iodoethylate with 1 g of orthopropionic ester in 1 ml of pyridine in a sealed tube for 1 hr at 150°. The dye was recrystallized from methanol. It formed a finely crystalline violet powder.

The styryl dye (X) was obtained by boiling 0.34 g of the iodoethylate with 0.15 g of dimethylaminobenzaldehyde in 5 ml of acetic anhydride for 25 min. It was purified by recrystallization from methanol. It formed violet needles.

SUMMARY

2-Methyloxazolo-(5,4-g)-benzthiazole was synthesized. It was shown that the 2,6-dimethyloxazolo-(4,5-f)-benzthiazole described in the literature is actually 2,7-dimethyloxazolo-(5,4-g)-benzthiazole. From the above base we prepared the iodoethylate and the following dyes: a monomethynecyanine, symmetrical, unsymmetrical, and meso-substituted carbocyanines, a merocyanine, and a styryl dye.

It was found that the addition of an oxazole ring to the benzthiazole nucleus has little effect on the absorption maximum of the dyes.

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REACTIONS OF AROMATIC NITRO COMPOUNDS

XII. NEW METHOD OF PREPARING ALKYL ETHERS OF 2,4-DINITROTHIOPHENOL

S. S. Gitis and Zh. P. Piskunova

Dnepropetrovsk State University

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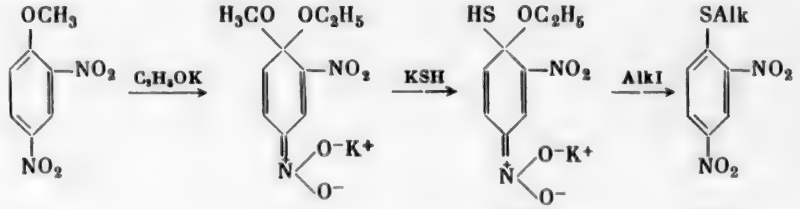
pp. 3400-3401, October, 1961
Original article submitted September 13, 1960

One of us showed previously [1] that 2,4-dinitroanisole cannot be obtained from 2,4-dinitrothioanisole by transetherfication. This compelled us to investigate the replacement of the methoxyl group in 2,4-dinitroanisole by a SCH_3 group. The ease of this replacement can evidently be explained by the fact that the process passes through the formation of reactive intermediate products of the quinol type.



(I) (II) (III) (IV)

In the presence of alcoholic alkali, dinitroanisole forms the intermediate product (II), which is attacked by sodium hydrosulfide to form the product (III). The latter most probably reacts with the alkyl halide to form the thioether. This hypothesis is confirmed by the fact that thioethers are not formed from a thiophenol and an alkyl halide in a solution of alkali in dioxane. Thus, reactive intermediates cannot be obtained in the absence of alcohol and therefore no thioethers are formed.

The method we propose excludes the formation of by-products, namely, the symmetrical tetranitro sulfide and the corresponding disulfide, which cannot be eliminated in Willgerodt's method [2]. In addition, the need for working with mercaptans, as was proposed by Bost et al. [3], is eliminated.

In our case, the alkyl ethers of 2,4-dinitrothiophenol were prepared in the cold. The method developed was applied to the preparation of trinitrothianisole and other polynitrothioethers.

EXPERIMENTAL

General method of preparing alkyl ethers of 2,4-dinitrothiophenol. A 0.0025 mole sample of 2,4-dinitroanisole was dissolved in 25 ml of alcohol with heating. This solution was cooled and a solution of 0.002 mole of potassium hydroxide in 5 ml of alcohol added. After the solution had ben kept for 15 min, 0.007 mole (16 ml of alcohol solution) of potassium hydrosulfide* was added. The solution was left for 2 hr, when the light red color changed to dark brown. At the end of this time, a further 0.004 mole of potassium hydroxide in 5 ml of alcohol and 0.007 mole of the alkyl iodide were added. After it had stood for 1 hr, the solution was diluted with water. The ethers were collected and recrystallized from ethanol and ligroin. In the case of the primary isobutyl ether of 2,4-dinitrothiophenol, the solution was diluted with water after it had stood for 15 min. The yields and constants of the ethers are given in the table.

SUMMARY

1. It was shown that the nucleophilic replacement of the methoxyl group in 2,4-dinitroanisole by a SCH_3 group proceeds in the cold.

* The alcohol solution of potassium hydrosulfide was prepared by Willgerodt's method [4].

Alkyl ethers of 2,4-dinitrothiophenol	Yield (%)	Melting point	
		our data	literature data [3]
Methyl	87	126°	128°
Ethyl	84	115	115
n-Propyl	58	81.5-82	81
n-Butyl	40	64-65	66
Primary isobutyl	40	79-80	76
n-Amyl	47	78-79	80
Primary isoamyl	44	72.5-73	59

2. A simple new method is proposed for the preparation of alkyl ethers of 2,4-dinitrothiophenol.

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SYNTHESIS OF SOME NEW AZINES

L. Ya. Malkes and L. V. Shubina

Kharkov Branch of the All-Union Scientific Research Institute of Chemical Reagents
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Original article submitted August 22, 1960

Aromatic azines of unsymmetrical (mixed) structure R − CH = N − N = CH − R' have been studied little [1-8].

We synthesized mixed azines with all combinations of the aryl radicals: phenyl, α-naphthyl, β-naphthyl, 4-biphenylyl, and 9-anthryl and also symmetrical 9-anthrylazine.

The azines were synthesized according to the following scheme.

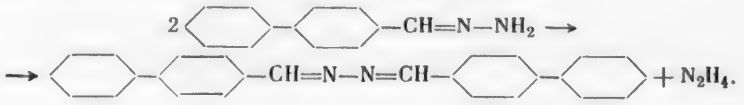
$$R-C(=O)H + H_2N-NH_2 \longrightarrow R-CH=N-NH_2 + H_2O$$

$$R-CH=N-NH_2 + R'-C(=O)H \longrightarrow R-CH=N-N=CH-R' + H_2O$$

For the preparation of the azines, we synthesized by known procedures [2, 9-14] with slight changes benzalhydrazone, α-naphthaldehyde, β-naphthaldehyde, 4-biphenylaldehyde, α-anphthalazine, β-naphthalazine, and 4-biphenylalazine.

In the first stage of the synthesis of the hydrazones, complications arose in their purification. Despite different variations in the conditions for preparing the hydrazones, azines were obtained in small amounts and contaminated them. With purification by recrystallization with heating, there was further decomposition of the hydrazone and the formation of the symmetrical azine.

While benzalhydrazone is quite a stable compound which can be distilled without decomposition [15], naphthalhydrazone and 4-biphenylalhydrazone are very sensitive to heating and even with gradual heating to 110-120°, there is a rearrangement which yields the symmetrical azine.



The color of the substance thereupon changes from slightly yellowish to yellow.

As a result of the instability of these hydrazones to thermal treatment, their melting points were determined on a block, which was preliminarily heated to a temperature 1° below the melting point of the hydrazone. The hydrazones obtained were dried in a vacuum desiccator for the same reason.

For the synthesis of the hydrazones we used a 20% excess of hydrazine hydrate, with which the formation of azines was found to be minimal.

α-Naphthalhydrazone was synthesized by boiling α-naphthalazine with hydrazine hydrate in the presence of dehydrating substances (barium oxide, calcium oxide, etc.).

Azines containing the radicals α-naphthyl, β-naphthyl, 4-biphenylyl, and 9-anthryl did not change in 3 months.

Mixed azines containing a phenyl radical together with α-naphthyl, β-naphthyl, 4-biphenylyl, and 9-anthryl radicals decomposed with a change in color and melting point. Thus, for example, benzal-(9-anthral)-azine changed from yellow to orange, forming a mixture of benzalazine and 9-anthralazine with m.p. 262°.

TABLE 1

R in R − CH = N−CH$_2$	Starting materials	Melting point	Yield (%)
α-$C_{10}H_7$	α-Naphthalazine (m.p. 150°) and hydrazine hydrate	91°	87.0
β-$C_{10}H_7$	β-Naphthalazine (m.p. 232°) and hydrazine hydrate	144	83.0
p-$C_6H_5C_6H_4$	4-Biphenylalazine (m.p. 245°) and hydrazine hydrate	147	82.0

A study of the properties of the mixed azines we obtained with various aromatic radicals confirmed the consideration put forward previously [8]. Thus, the unequal distribution of electron density in the system of conjugated bonds was most marked in azines with a phenyl radical at one carbon atom and a naphthyl, biphenylyl, or anthryl radical at the other, as a result of which there was weakening and rupture of the N − N bond with the formation of symmetrical products.

We checked the possibility of preparing benzal-(4-biphenylal)-azine by a method described previously [16-17]. As a result we obtained biphenylalazine (m.p. 242°) and a mixture of biphenylalazine with benzalazine (m.p. 203°). Thus, this method did not give positive results in the preparation of benzal-(4-biphenylal)-azine.

EXPERIMENTAL

Synthesis of Hydrazones

α-Naphthalhydrazone. A mixture of 3.08 g of α-naphthalazine (m.p. 150°) and 0.075 g of hydrazine hydrate was boiled for 1 hr. Then the reaction mixture was cooled and the crystalline product obtained washed with two portions (10 ml each) of anhydrous alcohol, collected, and dried in a vacuum desiccator. The weight of the hydrazone was 2.96 g. The slightly yellowish crystalline powder was readily soluble in benzene and dichloroethane, less soluble in alcohol, and insoluble in ligroin.

β-Naphthalhydrazone and 4-biphenylalhydrazone (Table 1) were synthesized analogously.

Synthesis of Azines

Benzal-(β-naphthal)-azine. A solution of 1.2 g of benzalhydrazone in 10 ml of anhydrous alcohol was added dropwise (at a rate of 1-2 drops per sec) with continuous stirring to a solution of 1.56 g of β-naphthaldehyde in 15 ml of anhydrous alcohol. When the hydrazone had been added, the reaction mixture was stirred for a further 2 hr. The azine was collected and washed on the filter with 5 ml of cooled anhydrous alcohol. The product was purified by two recrystallizations from 20 ml portions of dichloroethane. The azine was dried in a vacuum desiccator and weighed 2.3 g.

Benzal-(4-biphenylal)-azine, α-naphthal-(4-biphenylal)-azine, (4-biphenylal)-(9-anthral)-azine, (α-naphthal)-(β-naphthal)-azine, (α-naphthal)-(9-anthral)-azine, and benzal-(9-anthral)-azine (Table 2) were synthesized analogously.

In the synthesis of benzal-(9-anthral)-azine, after the preparation of the compound, the excess solvent was evaporated at room temperature. The azine obtained consisted of a yellow-orange crystalline powder. As the azine decomposed even when heated gently, its melting point could not be determined.

Benzal-(α-naphthal)-azine. To a solution of 0.55 g of benzaldehyde in 10 ml of anhydrous alcohol was added a solution of 0.85 g of α-naphthalhydrazone in 15 ml of anhydrous alcohol dropwise with continuous stirring. When the hydrazone solution had been added, the reaction mixture was stirred for 1 hr at room temperature and 30 min at 35-40°. At the end of the reaction, 50% of the alcohol was evaporated at room temperature. A voluminous yellow crystalline precipitate formed and this was collected, washed on the filter with 10 ml of cooled ligroin, and dried in a vacuum desiccator. Its weight was 1.1 g.

(4-Biphenylal)-(β-naphthal)-azine. A 0.91 g sample of 4-biphenylalhydrazone was dissolved in 50 ml of anhydrous alcohol. The hydrazone solution was added dropwise with continuous stirring to a solution of 0.8 g of β-naphthaldehyde in 30 ml of anhydrous alcohol. After approximately 30 min, the solution became turbid and a precipi-

TABLE 2

Aromatic azines R—CH=N—N=CH—R′		Starting materials	Solvents	M. p.	Yield (in %)	Empirical formula					
						found %			calculated %		
R	R′					C	H	N	C	H	N
1	2	3	4	5	6	7	8	9	10	11	12
β-$C_{10}H_7$	C_6H_5	Benzalhydrazone β-Naphthaldehyde	C_2H_5OH C_2H_5OH	121°	89	83.52	5.30	—	83.72	5.42	—
p-C_6H_5—C_6H_4	C_6H_5	4-Phenylbenzaldehyde Benzalhydrazone	C_6H_6 C_2H_5OH	147	89	84.22	5.18	9.85	84.50	5.62	10.14
9-$C_{14}H_9$	C_6H_5	9-Anthraldehyde Benzalhydrazone	C_6H_6 C_2H_5OH	—	85	84.88	5.67	9.46	85.23	5.36	9.06
α-$C_{10}H_7$	C_6H_5	Benzaldehyde α-Naphthalhydrazone	C_2H_5OH C_2H_5OH	75	87	84.03	5.20	—	83.72	5.42	—
α-$C_{10}H_7$	p-$C_6H_5C_6H_4$	α-Naphthalhydrazone 4-Phenylbenzaldehyde	C_2H_5OH C_6H_6	120	80	86.46	4.98	—	86.92	5.32	—
β-$C_{10}H_7$	p-$C_6H_5C_6H_4$	4-Biphenylalhydrazone β-Naphthaldehyde	C_2H_5OH C_2H_5OH	176	71	86.40	5.28	—	86.92	5.32	—
9-$C_{14}H_9$	p-$C_6H_5C_6H_4$	4-Biphenylalhydrazone 9-Anthraldehyde	C_6H_6 C_6H_6	254	74	87.38	5.29	—	87.50	5.20	—
9-$C_{14}H_9$	α-$C_{10}H_7$	α-Naphthalhydrazone 9-Anthraldehyde	C_2H_5OH C_6H_5	197	77	86.85	5.02	7.65	87.15	5.03	7.82
α-$C_{10}H_7$	β-$C_{10}H_7$	β-Naphthaldehyde α-Naphthalhydrazone	C_2H_5OH C_2H_5OH	136	75	85.17	5.68	8.67	85.23	5.36	9.06
9-$C_{14}H_9$	β-$C_{10}H_7$	β-Naphthalhydrazone 9-Anthraldehyde	C_2H_5OH C_6H_6	228	89	87.17	5.12	7.52	87.15	5.03	7.82
9-$C_{14}H_9$	9-$C_{14}H_9$	9-Anthraldehyde Hydrazine hydrate	C_6H_6 C_2H_5OH	267	86	—	—	6.73	—	—	6.86

tate began to form. The addition of the hydrazone was complete in 1 hr 45 min. The precipitate was left with the mother solution for 4 hr, then filtered, dried at 40-45°, and recrystallized twice from 15 ml portions of anhydrous benzene. The product weighed 1.22 g.

(β-Naphthal)-(9-anthral)-azine. A 1.7 g sample of β-naphthalhydrazone was dissolved in 75 ml of anhydrous alcohol. The hydrazone solution was added dropwise with continuous stirring to a solution of 2.06 g of 9-anthraldehyde in 25 ml of anhydrous benzene. The synthesis was carried out at room temperature. After the addition of approximately 20% of the aldehyde, a bright orange precipitate began to form. When the aldehyde solution had been added, the reaction mixture was stirred for a further 2 hr. The precipitate was then collected, dried in a vacuum desiccator and recrystallized twice, first from 35 ml of anhydrous benzene and then from 25 ml of dichloroethane. The product weighed 3.21 g.

9-Anthralazine. A solution of 4.12 g of 9-anthraldehyde in 25 ml of benzene was added dropwise with continuous stirring to a solution of 0.05 g of hydrazine hydrate in 25 ml of alcohol. When approximately 1/3 of aldehyde solution had been added, an orange-red precipitate began to form. When the aldehyde solution had been added, the mixture was boiled with stirring for a further 1.5 hr. The reaction mixture was then cooled to 5-8° and the azine collected and dried at 40-45°. The product was purified by recrystallization from 35 ml of benzene and then from 35 ml of dichloroethane. The product weighed 3.52 g.

SUMMARY

1. Eleven aromatic azines and three hydrazones that have not been described in the literature were synthesized.

2. It was established that mixed azines with a phenyl radical at one carbon atom and an α-naphthyl, β-naphthyl, 4-biphenylyl, or 9-anthryl radical at the other are unstable.

3. On the example of phenyl-(4-biphenylyl)-azine it was shown that mixed aromatic azines cannot be prepared by the action of hydrazine hydrate on a mixture of aromatic aldehydes.

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REACTION OF PURINE DERIVATIVES WITH PHOSPHOROUS ESTERS

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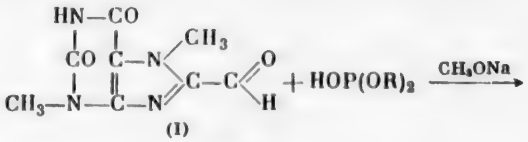
As a development of previous work on the synthesis of organophosphorus derivatives of caffeine [1, 2], we continued the investigation of the reactivity of a series of purine derivatives with dialkyl and trialkyl phosphites.

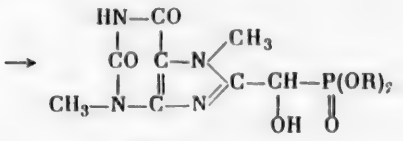
In the present work we attempted to replace the labile tertiary halogens [3] of 8-bromocaffeine [4] and 8-chloroisocaffeine [5] by a phosphonic group [$-PO(OR)_2$] by the Arbuzov and Michaelis – Becker reactions.

However, experiments on the treatment of 8-bromocaffeine by triisopropyl phosphite (with heating of the components to 190-210°) and sodium diethyl phosphite (with prolonged heating in toluene) did not give the expected results. It was not possible to introduce a diethyl- or diisopropylphosphonic radical directly into the purine nucleus of the imidazole ring and 8-isocaffeine.

When 8-theobromine aldehyde (I) was treated with dialkylphosphorous acids, addition occurred at the carbonyl group [6] of the aldehyde to form esters of α-hydroxy-8-methyltheobrominephosphinic acid.



(I)



(II)

The reaction occurred in the presence of sodium methylate as the catalyst and was accompanied by heat evolution.

We prepared the dimethyl, diethyl, diisopropyl, and diisobutyl esters of α-hydroxy-8-methyltheobromine-phosphinic acid (II). The experimental results are given in the table.

Ester (II) R	M.p.	Yield (%)	% P	
			found	calculated
CH_3	223—224°	50.4	9.97	9.74
C_2H_5	211—212	77.0	9.14	8.95
iso- C_3H_7	216	51.5	8.24	8.28
iso- C_4H_9	214—215	30.6	8.08	7.71

EXPERIMENTAL

8-Bromocaffeine (m.p. 205°) was obtained by Fischer's method [7]. 8-Theobrominealdehyde (m.p. 288-289°) was synthesized by the method developed by E. S. Golovchinskaya and her co-workers [8] by chlorination of 8-methyltheobromine* with subsequent hydrolysis of the 8-dichloromethyltheobromine.

Esters of α-hydroxy-8-methyltheobrominephosphinic acid. To a mixture of 8-theobromineladehyde (0.7-1.0 g) and the dialkylphosphorous acid (25% excess over the equimolecular amount) was added a saturated solution of sodium methylate (0.25 ml). The reaction proceeded with a rise in temperature from 8 to 30° with careful stirring of the mixture. To complete the reaction the mixture was rapidly heated to 90° on a boiling water bath.

All the esters were washed carefully with a small amount of cooled water, dried, and recrystallized (2-3 times) from anhydrous methanol. The diisobutyl ester was heated twice with activated charcoal in anhydrous ethanol.

The esters obtained were white crystalline substances, which dissolved readily in water (with the exception of the diisobutyl ester), hot methanol and ethanol, and glacial acetic acid, very sparingly in benzene, and not at all in ether.

SUMMARY

1. The active tertiary halogens in 8-bromocaffeine and 8-chloroisocaffeine are not replaced by a phosphonic radical even under drastic conditions.

2. The reaction of 8-theobrominealdehyde with dialkylphosphorous acids was studied. Esters of α-hydroxy-8-methyltheobrominephosphinic acid were synthesized.

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* We are very grateful to E. S. Golovchinskaya for providing 8-chloroisocaffeine and 8-methyltheobromine.

SYNTHESIS OF ESTERS OF α-HYDROXYPHOSPHONOBARBITURIC ACID

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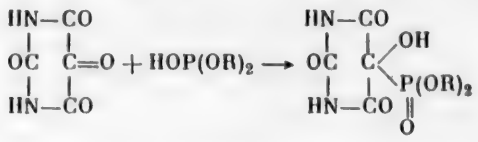
Some barbituric acid derivatives with alkyl, alkylene, and aryl radicals at the methylene carbon have a valuable application in medicine as soporifics. In this connection it seemed interesting to study the reaction of dialkylphosphorous acids with alloxan. The latter has the properties of a ketone and, consequently, one can expect the formation of esters of α-hydroxyphosphonobarbituric acid [1].



The literature contains descriptions of esters of phosphonoalkyl(aryl)barbituric acid and the diethyl ester of phosphonobarbituric acid, in which the phosphonic radical is connected directly to the methylene carbon of the pyrimidine ring, as in our case. These esters were synthesized by condensation of phosphonomalonic esters with urea [2].

Our experiments showed that esters of α-hydroxyphosphonobarbituric acid may be obtained readily by condensation of dialkylphosphorous acids with mesoxalylurea (alloxan).

The reaction of dialkyl phosphites with anhydrous alloxan proceeded with the evolution of heat. The thermal effect depended on the radical and the amount of acid taken. The greatest thermal effect was observed in the reaction with dimethylphosphorous acid.

We prepared the dimethyl, diethyl, dipropyl, diisopropyl, dibutyl, and diisobutyl esters of α-hydroxyphosphonobarbituric acid.

The results of the reactions of alloxan with dialkyl phosphites and the characteristics of the esters obtained are given in the table.

The esters synthesized were hydrolyzed readily by prolonged heating of their aqueous solutions.

EXPERIMENTAL

We prepared anhydrous alloxan by recrystallization of its monohydrate [3] from a mixture of glacial acetic acid and acetic anhydride (1 : 1) with subsequent heating for 30 min at 200-210° (on Wood's alloy) and a pressure of 1 mm. The orange crystals had m.p. 245-247°.

Esters of α-hydroxyphosphonobarbituric acid. To anhydrous alloxan was added the dialkylphosphorous acid (25% excess). The reaction began after careful mixing of components and was accompanied by a rise in temperature. For completion of the reaction, the mixture was heated for 1-2 min on a boiling water bath (apart from experiments with dimethylphosphorous acid) with continuous stirring. The reaction product was recrystallized 2-3 times from anhydrous ethanol.

Three experiments were carried out with dimethylphosphorous acid. In the first experiment with an equimolecular amount of the acid, the temperature rose from 19 to 220° and a largely polymeric product formed. In the second experiment with a 25% excess of the acid, the temperature rose from 24 to 190°; the yield of the ester was 60%. The thermal effect of the reaction was reduced by using a 50% excess of the acid (the data of the third experiment are given in the table).

R	Amount of reagents (g)		Thermal effect on mixing (temperature rise)	Thermal effect on heating (temperature rise)	Yield* (in %)	Melting point	% P	
	dialkylphosphorous acid	alloxan					found	calculated
CH_3	2.9	2.5	18—140°	—	65.0	189—190°	12.14	12.30
C_2H_5	2.4	2.0	17—32	32—130°	50.2	197—198	10.70	11.07
n-C_3H_7	2.92	2.0	22—40	40—100	62.2	193	9.67	10.06
iso-C_3H_7	2.92	2.0	16—45	45—100	32.0	193—194	10.38	10.06
n-C_4H_9	3.41	2.0	22—36	36—100	64.0	184	8.87	9.22
iso-C_4H_9	3.42	2.0	21—45	45—115	59.4	178—179	9.57	9.22

* The yields of the esters after the first recrystallization are given.

All the esters obtained were white crystalline substances, which were soluble in water (hot water in the case of the dipropyl ester), hot methanol, ethanol, and glacial acetic acid and slightly soluble in hot benzene and diethyl ether.

Aqueous solutions of the esters had an acid reaction (to Congo); evaporation of the water yielded pink crystalline residues with indefinite melting points.

SUMMARY

The reaction of dialkylphosphorous acids with anhydrous alloxan was studied. Esters of α-hydroxyphosphonobarbituric acid were synthesized.

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REACTION OF HEXAMETHYLDISILAZANE WITH ALUMINUM AND TITANIUM HALIDES METHOD OF SYNTHESIZING TRIALKYLHALOSILANES

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It is reported in the literature that aminodisilane reacts with hydrogen chloride to form chlorosilane and ammonium chloride [1].

$$(SiH_3)_2NH + 3HCl \longrightarrow 2SiH_3Cl + NH_4Cl.$$

There are also reports on the possibility of cleaving the silazane bond with BF_3 [2].

In the present work we investigated the reaction of hexamethyldisilazane with aluminum and titanium halides in order to prepare trimethylhalosilanes.

As the starting materials we used aluminum chloride, aluminum bromide, aluminum iodide, titanium tetrachloride, and hexamethyldisilazane. In the investigation it was established that hexamethyldisilazane reacts vigorously with aluminum and titanium halides according to the equations:

$$[(CH_3)_3Si]_2NH + AlX_3 \longrightarrow 2(CH_3)_3SiX + NHAlX$$
$$X = Cl, Br, I$$
$$[(CH_3)_3Si]_2NH + TiCl_4 \longrightarrow 2(CH_3)_3SiCl + NHTiCl_2$$

We developed a method of synthesizing trimethylchloro-, bromo-, and iodosilanes which consists simply of distillation of an equimolecular mixture of hexamethyldisilazane and aluminum and titanium halides. The yields of the trimethylhalosilanes were 70-88%. This method could evidently become a general method of preparing trialkylhalosilanes. The formation of trialkylhalosilanes probably proceeds through the intermediate formation of trialkylsilylaminoaluminum dihalides.

$$R_3SiNHSiR_3 + AlX_3 \longrightarrow R_3SiX + R_3SiNHAlX_2$$

EXPERIMENTAL

Synthesis of trimethylchlorosilane. a) Into a distillation flask with a fractionating head was placed 19 g of titanium tetrachloride and 16.1 g of hexamethyldisilazane was introduced slowly from a dropping funnel. The reaction proceeded with heat evolution. The reaction mixture was distilled to yield 19.1 g (88%) of trimethylchlorosilane with b.p. 57-58° and a chlorine content of 32.68%.

b) To 40 g of aluminum chloride was added 48.3 g of hexamethyldisilazane from a dropping funnel. The reaction mixture was distilled on a column with an efficiency of 10 theoretical plates to yield 48.0 g (73.7%) of trimethylchlorosilane with b.p. 58° and a chlorine content of 32.65%.

Synthesis of trimethylbromosilane. By the above procedure, from 26.6 g of aluminum bromide and 16.1 g of hexamethyldisilazane we obtained 23.3 g (76.1%) of trimethylbromosilane with b.p. 81° and a bromine content of 52.11%.

Synthesis of trimethyliodosilane. Into a distillation flask with a fractionating head were placed 3.0 g of aluminum powder and 50 ml of dry benzene and then 38.1 g of crystalline iodine was added in portions with gentle heating.

The benzene was removed completely by distillation and to the aluminum iodide obtained in this way was gradually added 16.1 g of hexamethyldisilazane. Distillation of the reaction mixture yielded 28.0 g (70%) of trimethyliodosilane with b.p. 102-106°. On redistillation, the product distilled at 106-107°.

SUMMARY

A method was developed for the synthesis of trimethylhalosilanes based on the reaction of hexamethyldisilazane with aluminum and titanium halides. This method may be a general method of preparing trialkylhalosilanes.

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REACTIONS OF PHOSPHINES

II. REACTIONS OF PRIMARY AROMATIC PHOSPHINES WITH ALDEHYDES AND KETONES

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As was shown previously, primary aliphatic phosphines react with aldehydes and ketones to form salts of quaternary phosphonium bases and phosphines [1]. It was also shown that these products may be used for the synthesis of other organophosphorus compounds [2]. In the present work we studied the reaction of primary aromatic phosphines with aldehydes and ketones and some properties of the substances obtained are described. The reaction was studied on the example of the reaction of phenylphosphine with formaldehyde, acetaldehyde, benzaldehyde, and acetophenone. It was found that like primary aliphatic phosphines, phenylphosphine reacts with formaldehyde in the presence of hydrochloric acid (molar ratios of 1 : 1 and 3 : 1) with the formation of phenyltrimethylolphosphonium chloride:

$$C_6H_5PH_2 + 3CH_2O + HCl \longrightarrow [C_6H_5P(CH_2OH)_3]^+\overline{Cl}.$$

The mechanism of this reaction consists of the repeated addition of a carbenium cation (methylol cation) to the phosphine and elimination of hydrogen chloride from the phosphonium salts obtained. The degree of alkylation depends on the nature of the aldehyde. Thus, phenylphosphine reacted with acetaldehyde and benzaldehyde to form only tertiary phosphines. The reaction of acetophenone with phenylphosphine also yielded a tertiary phosphine:

$$C_6H_5PH_2 + C_6H_5COCH_3 + HCl \longrightarrow C_6H_5{-}P\left(-\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-C_6H_5\right)_2.$$

The latter substance decomposed during vacuum distillation to form a secondary phosphine.

The possibility of adding to a phosphine two or three molecules of an aldehyde or ketone depends to a considerable extent on the electrophilicity of the groups in the phosphines obtained and their steric characteristics.

The products from the addition of phosphines to aldehydes and ketones tended to decompose. For example, phenyltrimethylolphosphonium chloride reacted with Schiff's reagent like aldehydes. Treatment of phenyltrimethylolphosphonium chloride with aqueous alkalis liberated hydrogen and, it must be assumed, formed phenyldimethylolphosphine oxide, which, however, could not be isolated in a discrete state. The reaction of the phosphonium salt with tertiary amines gave a good yield of phenyldimethylolphosphine. The cleavage of the phosphonium salts evidently proceeds by the mechanism we proposed for alkyltrimethylolphosphonium chloride [1]. All the tertiary phosphines obtained by this method were oxidized by nitrogen oxides to phosphine oxides:

$$C_6H_5P(CH_2OH)_2 \xrightarrow{N_2O_4} C_6H_5\overset{\displaystyle O}{\overset{\|}{P}}(CH_2OH)_2.$$

The action of methyl iodide on phenyldimethylolphosphine yielded phenyldimethylolmethylphosphonium iodide:

$$C_6H_5P(CH_2OH)_2 \xrightarrow{CH_3I} [C_6H_5\overset{\displaystyle CH_3}{\overset{|}{P}}(CH_2OH)_2]^+\overline{I}.$$

Phenyltrimethylolphosphonium chloride reacted with thionyl chloride to form phenyltri(chloromethyl)phosphonium chloride:

$$[C_6H_5P(CH_2OH)_3]^+\overline{Cl} \xrightarrow{SOCl_2} [C_6H_5P(CH_2Cl)_3]^+\overline{Cl}\bullet$$

EXPERIMENTAL

1. Phenyltrimethylolphosphonium chloride. To 32 ml of 30% formaldehyde and 8 ml of hydrochloric acid (d 1.17) was added 8 g of phenylphosphine with stirring in a stream of nitrogen. The reaction mixture was kept at 40° for 3 hr and then the excess formaldehyde and hydrochloric acid were removed in vacuum at 70-80°. We obtained 14.9 g (87%) of a thick oil. The oil was purified by solution in anhydrous methanol, treatment with animal charcoal, filtration of the solution, and removal of the solvent in vacuum. Phenyltrimethylolphosphonium chloride is soluble in water, alcohol, and acetic acid and insoluble in ether and benzene.

Found %: P 12.53; Cl 14.47. $C_9H_{14}O_3PCl$. Calculated %: P 13.09; Cl 14.96.

2. Phenyltri(chloromethyl)phosphonium chloride. To 2 g of phenyltri(methylol)phosphonium chloride was added 5 ml of thionyl chloride and the mixture heated at 90° for 5 hr. Removal of the excess thionyl chloride yielded 2 g of phenyltri(chloromethyl)phosphonium chloride (81.4% yield). The product was recrystallized from a mixture of methanol, ethyl acetate, and ether; it decomposed partly at 230° and had m.p. 236°. The product was soluble in alcohol, water, chloroform, and acetic acid and insoluble in ether and benzene.

Found %: P 10.50; Cl 47.70. $C_9H_{11}PCl_4$. Calculated %: P 10.61; Cl 48.58.

3. Phenyldi(methylol)phosphine. To 30 ml of triethylamine was added 9.5 g of phenyltri(methylol)phosphonium chloride with stirring in a stream of nitrogen and the mixture kept at 50° for 1 hr. After the triethylamine hydrochloride had been removed by filtration, the excess triethylamine was removed in vacuum. We obtained 5.7 g of phenyldi(methylol)phosphine as a thick, light yellow oil, which did not distill at 0.5 mm. The yield was 83%. The substance was soluble in alcohol, acetic acid, and chloroform and insoluble in water, benzene, ether, and ethyl acetate.

Found %: P 18.33, 18.02. $C_8H_{11}O_2P$. Calculated %: P 18.16.

4. Phenyldi(methylol)phosphine oxide. Nitrogen oxides diluted with nitrogen were passed through 4.6 g of phenyldi(methylol)phosphine. The oxidation was complete by the end of the second hour and the phosphine acquired a green color. For more complete oxidation, the phosphine was kept at 40-50° for 1 hr and then the nitrogen oxides were removed in vacuum. We obtained 4.37 g of phenyldi(methylol)phosphine oxide as a thick yellow oil. The yield was 89%. The product was soluble in alcohol and benzene and sparingly soluble in ligroin.

Found %: P 16.10. $C_8H_{11}O_3P$. Calculated %: P 16.65.

5. Phenyldi(methylol)methylphosphonium iodide. To 0.75 g of phenyldi(methylol)phosphine was added 5 ml of methyl iodide and the reaction mixture heated at 40° for 2 hr and then the excess methyl iodide removed by distillation. We obtained 0.9 g (65.7%) of a thick yellow oil. The product was soluble in water and acetic acid and insoluble in alcohol, ethyl acetate, chloroform, ether, and benzene.

Found %: P 8.96, 8.67. $C_{19}H_{11}O_2IP$. Calculated %: P 9.93.

6. Phenyldiethylolphosphine. This was obtained under conditions analogous to those in experiment 1. From 15 ml of acetaldehyde, 7 ml of hydrochloric acid (d 1.17), 6 g of phenylphosphine and 10 ml of aqueous methanol we obtained 8.6 g of an oil (79.2% yield). It had b.p. 86-87° (0.5 mm); n^{20}_D 1.5381, d_4^{20} 1.0186.

Found %: P 15.03, 14.97. $C_{10}H_{15}O_2P$. Calculated %: P 15.65.

7. Phenyldi(ethylol)phosphine oxide. Dry nitrogen oxides were passed through 1 g of phenyldi(ethylol)phosphine for 45 min and a vigorous reaction was observed. Removal of the excess nitrogen oxides in vacuum yielded an oil, which was soluble in water, alcohol, acetic acid, ethyl acetate, chloroform, ether, and benzene and insoluble in ligroin. The yield was 91% and the b.p. 100-103° (0.5 mm).

Found %: P 14.63, 14.43. $C_{10}H_{15}O_3P$. Calculated %: P 14.47.

8. Phenyldi(phenylmethylol)phosphine. This was obtained under conditions analogous to those in experiment 1. From 15.5 g of benzaldehyde, 6 ml of hydrochloric acid, 5 g of phenylphosphine, and 27 ml of methanol we obtained 15 g of a thick oil (86% yield). The substance had b.p. 140-143° (3 mm) and was soluble in absolute ether, benzene, and alcohol and insoluble in water.

Found %: P 8.92, 9.03. $C_{20}H_{19}O_2P$. Calculated %: P 9.60.

9. Phenyldi(phenylmethylol)phosphine oxide. Dry nitrogen oxides were passed for 3 hr through 3 g of phenyldi-(phenylmethylol)phosphine in 10 ml of dry carbon tetrachloride and then the mixture was left overnight. On the following day the reaction mixture had acquired a green color. Removal of the solvent and excess nitrogen oxides in vacuum yielded 2.8 g (89.15%) of a thick yellow oil with b.p. 147-150° (10^{-4} mm). The substance was soluble in alcohol, ether, and benzene and insoluble in water.

Found %: P 9.25, 8.86. $C_{20}H_{19}O_2P$. Calculated %: P 9.15.

10. Phenyldi(α-phenylethylol)phosphine. To 10 ml of acetophenone in 10 ml of absolute ether was added 4 ml of phenylphosphine in a stream of nitrogen. Hydrogen chloride was passed through the reaction mixture for an hour with the temperature kept at 40-50°. The removal of the ether and excess acetophenone by distillation yielded a white crystalline substance, which was soluble in benzene, alcohol, and chloroform and insoluble in ether, ligroin, and water. After recrystallization from a mixture of ligroin and anhydrous benzene, the substance had m.p. 105-107°.

Found %: P 8.40, 8.48. $C_{22}H_{23}O_2P$. Calculated %: P 8.82.

Analogous results were obtained when the reaction was carried out in an aqueous alcohol medium. The thick oil crystallized on standing. The product obtained was vacuum distilled and had b.p. 162-163° (4 mm); n^{20}_D 1.5863, d_4^{20} 1.0654.

Found %: P 12.75. $C_{14}H_{15}OP$. Calculated %: P 13.44.

According to analysis data, phenyldi(α-phenylethylol)phosphine decomposed on distillation to form phenyl(α-phenylethylol)phosphine.

SUMMARY

The reaction of phenylphosphine with formaldehyde, acetaldehyde, benzaldehyde, and acetophenone was studied and it was shown that it forms salts of phosphonium bases and phosphines. The salt phenyltrimethylolphosphonium chloride and the phosphines were used for preparing various derivatives.

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2,4,5-TRICHLOROPHENYL ESTERS OF METHYLTHIOPHOSPHINIC AND METHYLPHOSPHINIC ACIDS

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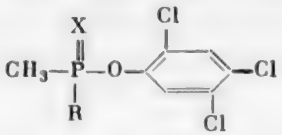
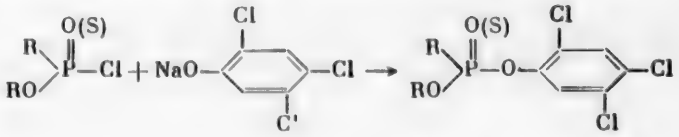
Recent communications on the high activity of O-2,4,5-trichlorophenyl esters of thiophosphoric acid [1] against cattle warble fly offers some hope of finding new agents against these afflictions of cattle among organophosphorus compounds. In the present work we prepared some organophosphorus compounds with a 2,4,5-trichlorophenol residue.



(I) X = O; R = alkoxyl (II) X = S; R = alkoxyl or NR'_2 (III) X = O; R = SC_3H_7-n

Substances of types (I) and (II) were obtained by the action of the acid chlorides of methylphosphinic and methylthiophosphinic acids in benzene on sodium 2,4,5-trichlorophenolate according to the scheme:



The substances synthesized were purified by distillation in high vacuum.

Compound (III) was synthesized by thermal isomerization of the corresponding thione isomer by prolonged heating in a stream of an inert gas.

The structure of O-2,4,5-trichlorophenyl S-n-propyl thiomethylphosphonate was demonstrated by physical and chemical methods. Thus, the infrared spectrum of the substance obtained contained a characteristic absorption band at 8.15 μ, which was undoubtedly caused by the valence vibrations of the phosphoryl bond (P = O). Treatment of O-2,4,5-trichlorophenyl S-n-propyl thiolomethylphosphonate with an aqueous alcohol solution of alkali with subsequent acidification gave quantitative yields of 2,4,5-trichlorophenol and methylphosphinic acid, mixed melting points of which with authentic samples of 2,4,5-trichlorophenol and methylphosphinic acid were not depressed.

The infrared spectra of distilled 2,4,5-trichlorophenyl esters of methylthionophosphinic acid (II) showed a weak absorption band in the region of 8.15 μ, which indicates a small amount of the thiol isomers. Hydrolysis of O-n-propyl O-2,4,5-trichlorophenyl thionomethylphosphonate yielded 2,4,5-trichlorophenol and the n-propyl ester of methylthiophosphinic acid. Consequently, during the distillation of the products (II) there was isomerization of thionomethylphosphonates to thiolomethylphosphonates (to a very slight extent).

Thus, it was shown that thermal isomerization of O-alkyl O-2,4,5-trichlorophenyl esters of thionomethylphosphinic acid may be used successfully for the synthesis of the corresponding thiolomethylphosphonates, whose preparation by other methods is difficult.

The O-alkyl and S-alkyl O-2,4,5-trichlorophenyl methylthiophosphonates obtained were colorless liquids, which were soluble in ether, alcohol, and benzene and insoluble in water. The properties of the substances synthesized are given in the table.

Properties of Substances of the Type $CH_3-\overset{\overset{X}{\|}}{P}(R)-O-C_6H_2Cl_3$ (2,4,5-trichlorophenyl)

Sample No.	R	X	Bath temperature	Pressure (mm)	n_D^{20}	d_4^{20}	Empirical formula	Yield (%)	Found (%)		Calculated (%)	
									P	Cl(S)	P	Cl(S)
1	OCH_3 *	S	170°	10^{-3}	1.5883	1.4680	$C_8H_8O_2PSCl_3$	43	10.05, 10.15	—	10.13	—
2	OC_3H_7-n	S	120	10^{-4}	1.5600	1.3510	$C_{10}H_{12}O_2PSCl_3$	67	9.33, 9.45	(9.35, 9.36)	9.35	(9.65)
3	OC_4H_9-n	S	140	10^{-4}	1.5569	1.3350	$C_{11}H_{14}O_2PSCl_3$	60	8.66, 8.89	(9.11, 9.26)	8.99	(9.24)
4	OC_4H_9-iso **	S	150	10^{-4}	1.5528	1.3200	$C_{11}H_{14}O_2PSCl_3$	54	8.71, 9.08	—	8.99	—
5	$N(C_2H_5)_2$	S	160	10^{-4}	1.5680	1.2635	$C_{11}H_{15}NOPSCl_3$	44	8.47, 8.38	—	8.90	—
6	OC_2H_5	O	153	10^{-4}	1.5383	1.3966	$C_9H_{10}O_3PCl_3$	51	9.98, 10.08	35.15, 35.08	10.24	34.76
7	OC_3H_7-n	O	162	10^{-4}	1.5190	1.3398	$C_{10}H_{12}O_3PCl_3$	32.5	10.21, 10.45	33.29, 33.41	9.83	33.12
8	OC_4H_9-n	O	170	10^{-4}	1.5043	1.3265	$C_{11}H_{14}O_3PCl_3$	23.5	9.57, 9.39	—	9.40	—
9	SC_3H_7-n	O	140	10^{-4}	1.5562	1.3528	$C_{10}H_{12}O_2PSCl_3$	40	9.47, 9.61	(9.87, 9.90)	9.35	(9.65)

* Found %: C 31.44, 31.75; H 2.77, 2.86. $C_8H_8O_2PSCl_3$. Calculated %: C 31.45; H 2.64.

** Found %: C 38.13, 38.42; H 4.18, 4.34. $C_{11}H_{14}O_2PSCl_3$. Calculated %: C 38.00; H 4.06.

EXPERIMENTAL

O-Methyl O-2,4,5-trichlorophenyl methylthionophosphonate* (typical preparation). With stirring and cooling with water, 8.6 g of the acid chloride of the methyl ester of methylthiophosphinic acid [2] was added slowly to 13 g of sodium 2,4,5-trichlorophenolate in 100 ml of anhydrous benzene. The reaction mixture was heated at 80° for 2.5 hr, cooled, and treated with 20% NaOH. The benzene layer was separated, washed with cold water until neutral, and dried over K_2CO_3, the benzene removed, and the residue distilled in high vacuum (10^{-3} mm) on a bath heated to 170°. The yield was 7.9 g (43%) and the product had d_4^{20} 1.4680, $n^{20}D$ 1.5883.

Hydrolysis of O-propyl O-2,4,5-trichlorophenyl methylthionophosphonate. A mixture of 3 g of O-n-propyl O-2,4,5-trichlorophenyl methylthionophosphonate and 5.4 g of NaOH in 50 ml of alcohol was boiled for 3 hr, the alcohol removed, and the residue acidified with a 10% solution of HCl. The crystalline mass was collected and washed several times with a small amount of water to yield 1.7 g (96%) of 2,4,5-trichlorophenol with m.p. 66° (according to literature data, 68.0° [3]). The filtrates were combined and evaporated, the residue extracted with ether, the solution dried over Na_2SO_4, and the ether evaporated to yield the monopropyl ester of methylthiophosphinic acid. The yield was 0.9 g (82%) and the product had $n^{20}D$ 1.4832 (according to literature data 1.4820 [2]).

Found %: S 21.18, 21.35. $C_4H_{11}O_2PS$. Calculated %: S 20.81.

S-n-Propyl O-2,4,5-trichlorophenyl methylthiolophosphonate. A 5 g sample of O-n-propyl O-2,4,5-trichlorophenyl methylthionophosphonate was heated at 170° for 10 hr and then at 200° in a stream of CO_2 for 4 hr, cooled, and distilled in high vacuum to yield 2 g (40%) of a substance with d_4^{20} 1.3528, $n^{20}D$ 1.5562. O-n-Propyl O-2,4,5-trichlorophenyl methylthionophosphonate was not isomerized by heating at 145-150° for 3-6 hr.

Hydrolysis of S-n-propyl O-2,4,5-trichlorophenyl methylthiolophosphonate. A mixture of 1.45 g of S-n-propyl O-2,4,5-trichlorophenyl methylthiolophosphonate and 1.95 g of NaOH in 15 ml of alcohol was boiled for 3 hr, the alcohol and some mercaptan removed by distillation, the residue acidified with 10% HCl, and the white precipitate collected, washed with water, and dried. The filtrate (with the odor of mercaptan) was evaporated, the residue treated with ether, the ether solution dried over Na_2SO_4, and the ether evaporated to yield methylphosphinic acid. The yield was 0.4 g (95%) and the m.p. 102-103° (according to literature data 104° [4]).

* The substances given in the table, with the exception of No. 9, were prepared analogously.

Acid chloride of the diethylamide of methylthionophosphinic acid. To 14.9 g of the diacid chloride of methylthiophosphinic acid [5] in 100 ml of anhydrous benzene was added 14.62 g of diethylamine dropwise at 10-12°. The reaction mixture was boiled for 40 min and cooled, the precipitate removed, and the residue after removal of the benzene vacuum distilled. The yield was 9.5 g (51%) and the product had b.p. 98-98.5° (3 mm), d_4^{20} 1.1507, $n^{20}D$ 1.5225.

Found %: Cl 19.30, 19.45. $C_5H_{11}PSCl$. Calculated %: Cl 19.10.

SUMMARY

1. Previously unknown thionophosphonates were prepared by the reaction of esters of acid chlorides of methylthiophosphinic acid with sodium 2,4,5-trichlorophenolate.

2. A method was developed for preparing O-2,4,5-trichlorophenyl S-alkyl thiolophosphonates by isomerization of O-2,4,5-trichlorophenyl O-alkyl thionomethylphosphonates at 170-200°.

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REACTIONS OF PHOSPHINES

III. REACTIONS OF SECONDARY PHOSPHINES WITH ALDEHYDES AND KETONES

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Primary aliphatic and aromatic phosphines react with aldehydes and ketones in the presence of acids to form salts of quaternary phosphonium bases and phosphines, depending on the ratio of the reagents, their nature, and the reaction conditions. In this way it is possible to obtain trihydric and dihydric phosphorus-containing alcohols and by simple rearrangements, glycols, which are at the same time phosphine oxides. These plyfunctional substances have a high reactivity. Alkyl- and aryldimethylolphosphine oxides react with monofunctional compounds (carboxylic acid chlorides, amines, etc. to form complex bis-substituted derivatives and with polyfunctional compounds to form polymeric substances. At the same time, in a number of cases it is necessary to prepare monosubstituted phosphines and phosphine oxides and the polyhydroxyphosphines, phosphine oxides, and phosphonium salts examined are unsuitable for this purpose. Naturally, for the preparation of such substances it is possible to use phosphines and phosphine oxides containing one hydroxyl group at a carbon atom of one organic radical attached directly to the phosphorus.

In the present work we studied the reaction of diarylphosphines with aldehydes and ketones for the above purpose. We studied the reaction of diphenyl phosphine with formaldehyde, acetaldehyde, benzaldehyde, and acetophenone.

The experiments showed that diphenylphosphine reacts readily with aldehydes and ketones. Thus, diphenylphosphine reacted with formaldehyde in the presence of hydrochloric acid to form diphenyldimethylolphosphonium chloride.

$$(C_6H_5)_2PH + 2CH_2{=}O + HCl \longrightarrow [(C_6H_5)_2P(CH_2OH)_2]^+\overline{Cl}$$

The reaction of diphenylphosphine with acetaldehyde was analogous under the same conditions and with the same reagent ratio. The action of benzaldehyde and acetophenone on diphenylphosphine formed tertiary phosphines, namely, diphenyl(phenylmethylol)phosphine and diphenyl(α-phenylethylol)phosphine. This was caused by the high electrophilicity of the phenylmethylol and phenylethylol groups, which leads to the displacement of the free electron pair of the phosphorus of the phosphines and the loss of the latter's basic properties. It must be assumed that the degree of alkylation of the diphenylphosphine is also affected by the steric properties of the reagents. The solvent also has some effect on the reaction of diphenylphosphine with aldehydes.

Thus, diphenylphosphine reacted with benzaldehyde in an aqueous alcohol medium in the presence of a molar amount of acid to form diphenyldi(phenylmethylol)phosphonium chloride. Diphenylphosphine reacted with aldehydes and ketones to form only tertiary phosphines if the reaction was carried out in an organic solvent in the presence of hydrogen chloride.

The reaction of diphenylphosphine with aldehydes and ketones evidently proceeds by a mechanism which consists of alkylation by carbenium cations and cleavage of the phosphonium salts formed with the liberation of hydrogen chloride, i.e., as we showed previously [1].

Phosphonium chlorides are reactive substances. They are converted into tertiary phosphines by the action of tertiary amines. When one of the phosphonium chlorides is treated with thionyl chloride, the hydroxyl is replaced by chlorine to give the corresponding chloro derivative.

The methylolphosphines obtained were oxidized readily and quantitatively by nitrogen oxides (N_2O_4) to form diphenylmethylolphosphine oxides, in which the hydroxyl may be replaced by various atoms and groups of atoms as in

the starting phosphonium salt. Thus, the action of diethylamine on diphenylmethylolphosphine oxide yielded diphenyldiethylaminomethylenephosphine oxide.

$$(C_6H_5)_2\overset{\overset{O}{\|}}{P}(CH_2OH) + HN(C_2H_5)_2 \longrightarrow (C_6H_5)_2\overset{\overset{O}{\|}}{P}-CH_2-N(C_2H_5)_2$$

Diphenyldimethylolphosphonium salts and diphenylmethylolphosphine oxide tend to decompose. Thus, these compounds give a positive reaction for aldehyde with Schiff's reagent.

EXPERIMENTAL

1. Diphenyldimethylolphosphonium chloride. With stirring in a stream of nitrogen, 6.5 g (0.039 mole) of diphenylphosphine was added to 15 ml (0.17 mole) of 34% formaldehyde and 9 ml (0.081 mole) of hydrochloric acid (d 1.17) at 20°. After the reaction mixture had been kept at 40° for 2 hr, the water was removed at 10 mm and 50-55°. We obtained 11.1 g (98.5%) of a thick oil. The oil was dissolved in absolute methanol, animal charcoal added, and the mixture shaken and filtered. The methanol was then removed from the filtrate in vacuum to yield a white crystalline substance with m.p. 165-166° (after reprecipitation from acetic acid with absolute ether). The substance was solutble in water, alcohol, and acetic acid, and sparingly soluble in organic solvents.

Found %: P 11.37; Cl 12.08. $C_{14}H_{16}O_2PCl$. Calculated %: P 10.95; Cl 12.52.

2. Diphenyldi(chloromethyl)phosphonium chloride. A mixture of 2 g (0.007 mole) of diphenyldimethylolphosphonium chloride and 10 ml of thionyl chloride was heated at 60-70° for 5 hr. Removal of the excess thionyl chloride in vacuum yielded an oil, which was dissolved in absolute methanol and precipitated with absolute ether. We obtained 1.2 g of a white crystalline substance, which was soluble in water, alcohol, and acetic acid. It had m.p. 217° after recrystallization from a mixture of absolute methanol, ethyl acetate, and absolute ether.

Found %: P 10.24; Cl 33.72. $C_{14}H_{14}PCl_3$. Calculated %: P 9.69; Cl 33.28.

3. Diphenylmethylolphosphine. A mixture of 8 g (0.028 mole) of diphenyldimethylolphosphonium chloride and 30 ml of dry triethylamine was stirred first at room temperature for 30 min and then at 70-80° for 3 hr. The precipitate of triethylamine hydrochloride was removed by filtration and washed with absolute ether. The triethylamine and absolute ether were removed from the filtrate in vacuum to yield 5.75 g (94%) of an oil. It had b.p. 113° (1 mm), n_D^{20} 1.6137, d_4^{20} 0.9316. The substance was soluble in all organic solvents and insoluble in water.

Found %: P 15.19. $C_{13}H_{13}OP$. Calculated %: P 14.32.

4. Diphenylmethylolphosphine oxide. Nitrogen oxides in a stream of dry nitrogen were passed through 2 g (0.009 mole) of diphenylmethylolphosphine* at 0° for 30 min and at 20° for 2 hr. Toward the end of the oxidation, the reaction mixture acquired a green color. Removal of the excess nitrogen oxides by flushing with dry nitrogen and keeping the reaction mixture in vacuum left an oil, which crystallized when absolute ether was added. We obtained 1.5 g (70%) of a substance with m.p. 192-193° (after recrystallization from a mixture of anhydrous benzene and ethyl acetate). The substance was soluble in alcohol and acetic acid and insoluble in water and ether.

Found %: P 14.09. $C_{13}H_{13}O_2P$. Calculated %: P 13.35.

5. N,N-Diethylaminomethyldiphenylphosphine oxide. A mixture of 0.5 g (0.002 mole) of diphenylmethylolphosphine oxide and 12 ml of diethylamine was heated and stirred at 60-70° for 3 hr. The precipitate was then collected and washed with absolute ether. The yield of the aminophosphine oxide was quantitative. The product had m.p. 147-151° (after recrystallization from a mixture of anhydrous ethyl acetate and benzene) and was soluble in water and alcohol and less soluble in organic solvents.

Found %: P 10.06; N 4.56. $C_{17}H_{22}ONP$. Calculated %: P 10.78; N 4.87.

6. Diphenyldi(ethylol)phosphonium chloride. Dry hydrogen chloride was passed through 1 g (0.006 mole) of diphenylphosphine and 5 ml (0.089 mole) of acetaldehyde in 15 ml of absolute ether. As the solution was saturated, there formed a white crystalline precipitate, which dissolved completely when hydrogen chloride was passed for a

* The oxidation could be carried out in dry CCl_4, but in this case the oxidation process was considerably protracted.

long time. The precipitate obtained was collected and washed with absolute ether. We obtained 1.5 g (78%) of the substance. The product was purified by solution in anhydrous methanol, the addition of animal charcoal, and shaking. Filtration and the addition of absolute ether to the solution yielded a pure product with m.p. 139-140°. The substance was soluble in water and alcohol and insoluble in organic solvents. It had a very unpleasant odor.

Found %: P 9.89; Cl 11.43. $C_{16}H_{20}O_2PCl$. Calculated %: P 9.97; Cl 11.40.

The same product was obtained by the reaction of diphenylphosphine with acetaldehyde in an aqueous alcohol medium in the presence of hydrochloric acid.

7. Diphenyl(phenylmethylol)phosphine. This was obtained under conditions analogous to those described in synthesis 6. From 1 g (0.006 mole) of diphenylphosphine and 3 ml (0.02 mole) of benzaldehyde in 10 ml of absolute ether we isolated an oil, which crystallized when triturated with a mixture of anhydrous methanol and absolute ether. We obtained 1 g of a white crystalline substance with m.p. 186°, which was soluble in alcohol, ethyl acetate, and acetic acid and insoluble in water.

Found %: P. 10.25. $C_{19}H_{17}OP$. Calculated %: P 10.59.

8. Diphenyldi(phenylmethylol)phosphonium chloride. With stirring in a stream of nitrogen, 4 g (0.02 mole) of diphenylphosphine was added to 10 ml (0.09 mole) of benzaldehyde and 5 ml (0.05 mole) of hydrochloric acid (d 1.17) in 25 ml of aqueous methanol. The reaction proceeded with appreicable heat evolution. The reaction mixture was kept at 40-50° for 3 hr and then the solvent was removed in vacuum. We obtained 10.4 g (98%) of a thick oil. The oil obtained was purified by solution in anhydrous methanol, the addition of animal charcoal, shaking, filtration, and removal of the methanol in vacuum. The substance was soluble in alcohol and benzene.

Found %: P 7.50, 7.40; Cl 8.48, 8.68. $C_{26}H_{24}O_2PCl$. Calculated %: P 7.12; Cl 8.17.

9. Diphenyl(α-phenylethylol)phosphine. This was obtained under conditions analogous to those described in experiment 8. From 12 ml (0.1 mole) of acetophenone, 5 ml (0.04 mole) of hydrochloric acid (d 1.17) in 5 ml of methanol, and 4 g (0.018 mole) of diphenylphosphine we obtained 4.8 g (84.5%) of a white crystalline substance. The product had m.p. 116-116.5° and was soluble in alcohol and acetic acid and insoluble in ether and benzene.

Found %: P 9.77. $C_{20}H_{19}OP$. Calculated %: P 10.11.

Analogous results were obtained by passing hydrogen chloride into a mixture of acetophenone and diphenylphosphine in absolute ether.

SUMMARY

1. It was established that diphenylphosphine reacts with formaldehyde, acetaldehyde, benzaldehyde, and acetophenone in the presence of hydrochloric acid to form diphenyldimethylolphosphonium salts and phosphines.

2. It was shown that treatment of a diphenyldimethylolphosphonium salt with tertiary amines gives a quantitative yield of phosphines, which are readily oxidized to methylolphosphine oxides.

3. The diphenyldimethylolphosphonium salts and methylolphosphine oxides were used for preparing various organophosphorus compounds.

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1. K. A. Petrov and V. A. Parshina, ZhOKh, 30, 784 (1960).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

REACTIONS OF PHOSPHINES

IV. PROPERTIES OF METHYLOLPHOSPHONIUM CHLORIDES AND METHYLOLPHOSPHINES

K. A. Petrov and V. A. Parshina

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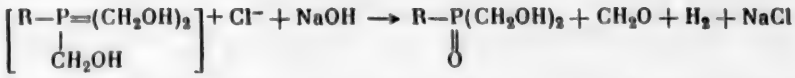
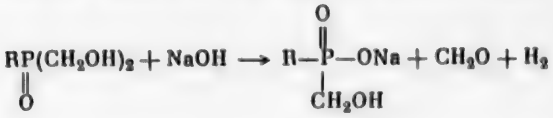
We showed previously that primary aliphatic phosphines react readily with aldehydes and ketones in the presence of hydrogen chloride and hydrochloric acid to form salts of secondary phosphines and quaternary phosphonium bases and phosphines [1]. We also studied the chemical properties of the products obtained. It was found that the latter may be used for the synthesis of various organophosphorus compounds.

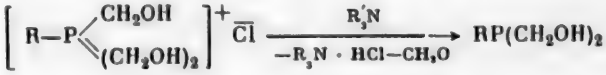
An interesting property of these products is their tendency to decompose. Thus, aldehyde derivatives of phosphines give a positive reaction for aldehydes with Schiff's reagent. Treatment of salts of quaternary phosphonium bases with aqueous alkalis led to the formation of tertiary phosphine oxides with the liberation of hydrogen and an aldehyde.



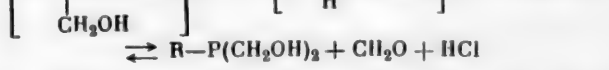
Treatment of an alkyldimethylolphosphine oxide with alkalis under more drastic conditions eliminated a hydrogen molecule and an aldehyde and formed salts of secondary phosphinic acids.



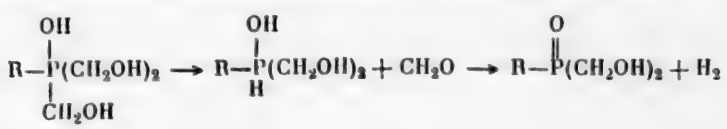
The action of tertiary amines on salts of quaternary phosphines gave good yields of tertiary phosphines.



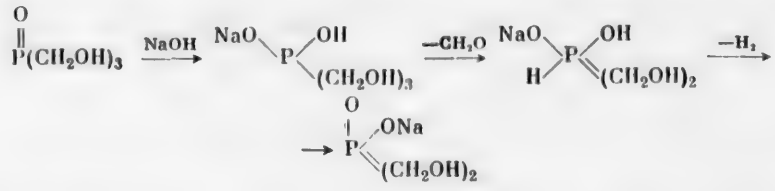
To explain all the reactions listed from a general point of view it is necessary to assume that the addition products of phosphines to aldehydes and ketones coexist with their cleavage products in reversible equilibria.



The equilibrium is displaced from let to right under various conditions by various methods. In the treatment of salts with alkalis, an unstable hydroxide with pentacovalent phosphorus is broken down.



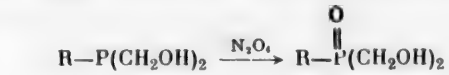
When a phosphine oxide is treated with alkali under more drastic conditions, a molecule of formaldehyde and hydrogen are also eliminated and a phosphinic acid is formed. In this case there is evidently addition of a molecule of alkali to the oxide at the phosphoryl group, after which the addition product with pentacovalent phosphorus decomposes. This reaction was studied previously on the example of trimethylolphosphine oxide [2]. Cleavage occurred on heating with sodium carbonate or barium hydroxide and dimethylolphosphinic acid was isolated as the barium salt.



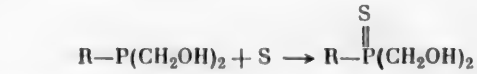
Hydrogen was also liberated when an alkyldimethylolphosphine oxide was heated with alkali. However, we were unable to isolate an alkylmethylolphosphinic acid in a discrete state.

In the treatment of addition products of phosphines and aldehydes with tertiary amines, the displacement of the above equilibrium is promoted by their binding of hydrogen chloride.

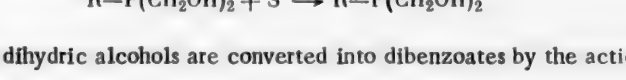
We also studied some reactions of cleavage products of salts of quaternary phosphonium bases. Thus, tertiary phosphines are oxidized by nitrogen oxides to phosphine oxides in quantitative yield.



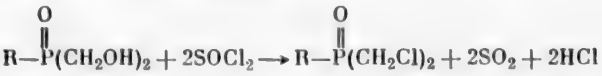
Heating phosphines with sulfur yields alkyldimethylolphosphine sulfides.



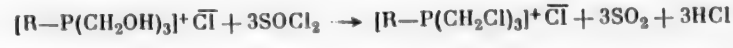
Phosphine oxides that are dihydric alcohols are converted into dibenzoates by the action of benzoyl chloride in the presence of tertiary amines.



When the phosphine oxides are treated with thionyl chloride, the hydroxyl group is readily replaced by chlorine to give good yields of halogen derivatives of phosphine oxides.



Thionyl chloride reacts analogously with the starting quaternary phosphonium salts.



Alkyltri(α-chloroalkyl)phosphonium chlorides are colorless substances, which crystallize readily from a mixture of ethyl acetate and anhydrous alcohol.

EXPERIMENTAL

Propyldimethylolphosphine. A mixture of 11.5 g of propyltrimethylolphosphonium chloride and 30 ml of dry triethylamine was stirred in a stream of nitrogen at room temperature for 30 min and then at 60° for 2 hr. The precipitate of triethylamine hydrochloride was removed by filtration and washed with absolute ether. The excess triethylamine and absolute ether were distilled from the filtrate. We obtained 6.83 g (87.8%) of a light yellow oil with b.p. 84° (1 mm), $n^{20}D$ 1.5061, d_4^{20} 1.0690. The substance was soluble in water, alcohol, and benzene.

Found %: P 22.98, 23.11. $C_5H_{13}O_2P$. Calculated %: P 22.75.

Propyldimethylolmethylphosphonium iodide. To 0.5 g of propyldimethylolphosphine was added 4 ml of methyl iodide. The reaction began very vigorously at 20° and then the reaction mixture was kept at 40° for 3 hr, after which the excess methyl iodide was removed in vacuum. We obtained 0.6 g of a thick yellow oil.

Found %: P 11.13, 10.37. $C_6H_{15}O_2PI$. Calculated %: P 11.13.

Propyldimethylolphosphine oxide. a) Dry nitrogen oxides diluted with nitrogen were passed through 2.2 g of propyldimethylolphosphine at 0° for 1.5 hr (until the oil acquired a green color). The excess nitrogen oxides were removed at first with a stream of nitrogen and then by heating in vacuum. We obtained a quantitative yield of an oil, which crystallized and distilled at 110-113° (10^{-4} mm).

Found %: P 20.30. $C_5H_{13}O_3P$. Calculated %: P 20.37.

b) A mixture of 23 g of propyltrimethylolphosphonium chloride and 35 g of barium hydroxide octahydrate in 120 ml of water was stirred for 3 hr while the temperature was gradually raised to 60°. The color of the reaction mixture changed to light brown. The excess barium ions were then removed in the form of the sulfate. Evaporation of the aqueous filtrate gave a brown oil, which was distilled. It had b.p. 110-113° (10^{-4} mm). We obtained 5.4 g of an oil, which crystallized to give a white crystalline substance with m.p. 87-88° (after two recrystallizations from a mixture of absolute ether and ligroin). The substance was soluble in benzene, ethyl acetate, water, and chloroform and less soluble in absolute ether. Analyses of the oily and crystalline substances gave identical results.

Found %: P 20.72. $C_5H_{13}O_3P$. Calculated %: P 20.37.

Propyldimethylolthiophosphine oxide. To 1.2 g of propyldimethylolphosphine was added 0.32 g of sulfur in portions with stirring in a stream of nitrogen. There was strong heat evolution by the reaction mass, which was then kept at 70-80° for 1 hr with continuous stirring. The product had b.p. 135-137° (2 mm) and was soluble in alcohol and benzene.

Found %: P 17.52; S 18.02. $C_5H_{13}O_2SP$. Calculated %: P 18.41; S 19.10.

Propyldimethylolphosphine oxide dibenzoate. To 5 ml of benzoyl chloride in 12 ml of anhydrous benzene was added 1 g of propyldimethylolphosphine oxide in 5 ml of anhydrous pyridine and then the reaction mixture was kept at 60-70° for 3 hr. The precipitate pyridine hydrochloride was then removed by filtration and the filtrate evaporated in vacuum. We obtained a yellow oil, which crystallized and was purified by solution in absolute ether, the addition of animal charcoal, shaking, and then removal of the ether in vacuum. The substance was soluble in ether, benzene, and ethyl acetate and insoluble in water.

Found %: P 8.38. $C_{19}H_{21}O_5P$. Calculated %: P 8.61.

Propyldi(chloromethyl)phosphine oxide. To 0.5 g of propyldimethylolphosphine oxide in 5 ml of benzene was gradually added 5 ml of thionyl chloride with stirring, when a vigorous reaction was observed. The reaction mixture was kept at the boiling point of the thionyl chloride for 4 hr and then the excess thionyl chloride was removed in vacuum. We obtained a brown oil with b.p. 73-75° (5 mm). The substance was soluble in organic solvents.

Found %: P 16.74; Cl 38.43. $C_5H_{11}OPCl_2$. Calculated %: P 16.39; Cl 37.52.

Propyltrichloromethylphosphonium chloride. A mixture of 1.01 g of propyltrimethylolphosphonium chloride and 5 ml of thionyl chloride was boiled for 9 hr and then the excess thionyl chloride removed in vacuum. We obtained 1.1 g of a white crystalline product with m.p. 197-197.5° (after two recrystallizations from a mixture of anhydrous ethyl acetate and methanol). The substance was soluble in water, alcohol, and chloroform and insoluble in ether and benzene.

Found %: P 11.78; Cl 54.39. $C_6H_{13}PCl_4$. Calculated %: P 12.02; Cl 54.98.

SUMMARY

A study was made of the decomposition of alkyltrimethylolphosphonium chlorides by alkaline reagents to the corresponding phosphines and phosphine oxides. It was shown that alkyldimethylolphosphines and phosphine oxides are very reactive substances.

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1. K. A. Petrov and V. A. Parshina, ZhOKh, 30, 784 (1960).
2. A. Hoffman, J. Am. Chem. Soc. 52, 2995 (1930).

ALKYL ESTERS OF N-DIALKOXY- AND N-DIAROXYPHOSPHINYL-IMINOCARBOXYLIC ACIDS

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The action of dry sodium alcoholates or solutions of sodium alcoholates in the corresponding alcohols on acid chlorides of N-dichloro- and N-diaroxyphosphinyliminocarboxylic acids (cf. [1]) formed (method A) alkyl esters of N-dialkoxy- and N-diaroxyphosphinyliminocarboxylic acids.

$$ArC(=NPOCl_2)Cl \xrightarrow{+3NaOR} ArC=[NPO(OR)_2]OR$$
$$ArC[=NPO(OAr')_2]Cl \xrightarrow{+NaOR} ArC[=NPO(OAr')_2]OR$$

The reaction also occurred when these acid chlorides were treated with alcohols in the presence of triethylamine, but the yields were lower (method B).

The alkyl esters of N-dialkoxyphosphinyliminocarboxylic acids (Table 1) were thick oils or low melting crystalline substances of a neutral nature, which could not be distilled at 15 mm without decomposition. Alkyl esters of N-diaroxyphosphinyliminocarboxylic acids (Table 2) were comparatively low-melting crystalline substances. Neither type of ester was hydrolyzed by water at room temperature (cf. [2]) or by brief boiling. When the methyl esters of N-dialkoxy- and N-diaroxyphosphinyliminocarboxylic acids were treated with ammonia in alcohol, the methoxyl group at the carbon atom was readily replaced by an amino group (cf. [3]) and the corresponding N-dialkoxy- and N-diaroxyphosphinylareneamidines were formed.

$$ArC[=NPO(OR)_2]OCH_3 + NH_3 \longrightarrow ArC[=NPO(OR)_2]NH_2$$

It was found previously that the action of alcohols in the absence of bases on trichlorophosphazosulfonaryls forms trialkoxyphosphazosulfonaryls and diesters of arylsufonylamidophosphoric acids [4], while the action of alcohols on trichlorophosphazoacyls yields diesters of acylamidophosphoric acids [5]. It was to be expected therefore that the reaction of alcohols with acid chlorides of N-dichlorophosphinyliminocarboxylic acids would form alkyl esters of N-diaroxyphosphinyliminocarboxylic acids or diesters of acylamidophosphoric acids. However, these assumptions were not justified. In actual fact, when acid chlorides of N-diaroxyphosphinyliminocarboxylic acids were treated with alcohols there was cleavage of the molecule and the formation of ammonium chloride, the ester of the corresponding carboxylic acid, an alkyl halide, and derivatives of phosphoric acid, which were readily soluble in water and alcohols, according to the scheme:

$$ArC(=NPOCl_2)Cl + 5ROH \longrightarrow NH_4Cl + 2RCl + HOPO(OR)_2 + ArCOOR$$

The only exception found up to now is the reaction of alcohols with the acid chloride of N-dichlorophosphinyl-3,5-dinitroiminobenzoic acid, which forms esters of N-dialkoxyphosphinyl-3,5-dinitroiminobenzoic acid.

$$3,5\text{-}(NO_2)_2C_6H_3C(=NPOCl_2)Cl + 3ROH \longrightarrow 3HCl +$$
$$+ 3,5\text{-}(NO_2)_2C_6H_3C[=NPO(OR)_2]OR$$

Acid chlorides of N-diaroxyphosphinyliminocarboxylic acids react with alcohols to give diesters of aroylamidophosphoric acids and alkyl halides.

$$ArC[=NPO(OAr')_2]Cl + ROH \longrightarrow RCl + ArCONHPO(OAr')_2$$

TABLE 1. Alkyl Esters of N-Dialkoxyphosphinyliminocarboxylic Acids of the Type ArC[=NPO(OR)$_2$]OR

Ar	R	Yield (%) preparation method	M. p.	External form and recrystallization solvent	Found (%)	Formula	Calculated (%)	Solubility*			
								alcohol	benzene	ether	acetone
C_6H_5	CH_3	96 (A) 79 (B)	—	Thick liquid	P 13.01, 13.05	$C_{10}H_{14}O_4NP$	P 12.74	± ±	+	−	± ±
C_6H_5	C_2H_5	84 (A)	—	Thick liquid	P 10.40	$C_{13}H_{20}O_4NP$	P 10.85	± ±	+	−	± ±
p-ClC_6H_4	CH_3	83 (A)	—	Thick liquid	P 11.13, 11.11	$C_{10}H_{13}O_4NPCl$	P 11.16	± ±	+	−	± ±
p-ClC_6H_4	C_2H_5	80 (A)	—	Thick liquid	P 9.53, 9.81	$C_{13}H_{19}O_4NPCl$	P 9.68	± ±	+	−	± ±
p-$NO_2C_6H_4$	CH_3	90 (A)	94—95°	Prisms, alcohol	N 9.63, 9.83	$C_{10}H_{13}O_6N_2P$	N 9.72	+	+	=	+
p-$NO_2C_6H_4$	C_2H_5	91 (A)	—	Thick, liquid	N 8.00, 8.05	$C_{13}H_{19}O_6N_2P$	N 8.48	+	+	=	+
3,5-$(NO_2)_2C_6H_3$	CH_3	82 (A) 76 (B) 80 **	106—108	Prisms, alcohol	N 12.81, 12.96	$C_{10}H_{12}O_8N_3P$	N 12.61	+	−	=	+
3,5-$(NO_2)_2C_6H_3$	C_2H_5	90 **	89—91	Prisms, alcohol	N 11.81, 11.96	$C_{13}H_{18}O_8N_3P$	N 11.20	+	−	=	+
3,5-$(NO_2)_2C_6H_3$	iso-C_3H_7	80 (B) 85 **	166—168	Prisms, alcohol	N 10.46, 10.41	$C_{16}H_{24}O_8N_3P$	N 10.07	+	−	=	+

* ±) Readily soluble at 20°; +) readily soluble at boiling point; −) difficultly soluble at boiling point; =) insoluble at boiling point. None of the substances were soluble in water, ligroin, or carbon tetrachloride.

** Yield from the action of the alcohol on the acid chloride of N-dichlorophosphinyl-3,5-dinitroiminobenzoic acid.

TABLE 2. Alkyl Esters of N-Diaroxyphosphinyliminocarboxylic Acids of the Type $ArC[=NPO(OAr')_2]OR$

Ar	Ar'	R	Yield (%) preparation method	M. p.	External form and recrystallization solvent	Found (%)	Formula	Calculated (%)	Solubility *			
									alcohol	benzene	ether	acetone
C_6H_5	C_6H_5	CH_3	70 (B)	144—146°	Plates, alcohol	P 8.26, 8.39	$C_{20}H_{18}O_4NP$	P 8.43	+	+	+	+ +
C_6H_5	C_6H_5	C_2H_5	92 (A)	138—140	Prisms, benzene	P 8.15, 8.35	$C_{21}H_{20}O_4NP$	P 8.12	+ +	+	+	+ +
p-ClC_6H_4	C_6H_5	CH_3	96 (A) 80 (B)	140—142	Prisms, alcohol	P 7.71, 7.80	$C_{20}H_{17}O_4NPCl$	P 7.71	+	+	+	+
p-ClC_6H_4	p-ClC_6H_4	CH_3	80 (A)	105—106	Prisms, alcohol	Cl 23.38, 23.26	$C_{20}H_{15}O_4NPCl_3$	Cl 22.60	+	+	−	+
p-$NO_2C_6H_4$	C_6H_5	CH_3	82 (A)	80—82	Prisms, alcohol	N 6.68 6.64	$C_{20}H_{17}O_6N_2P$	N 6.79	−	−	=	+
3,5-$(NO_2)_2C_6H_3$	C_6H_5	C_2H_5	93 (A) 71 (B) 90 **	111—113	Prisms, alcohol	N 8.89, 8.85 P 6.51, 6.30	$C_{21}H_{18}O_8N_3P$	N 8.92; P 6.57	−	−	=	+
3,5-$(NO_2)_2C_6H_3$	C_6H_5	iso-C_3H_7	98 **	115—117	Prisms, alcohol	N 8.44, 8.57	$C_{22}H_{20}O_8N_3P$	N 8.65	−	−	=	+
3,5-$(NO_2)_2C_6H_3$	p-$NO_2C_6H_4$	CH_3	96 **	199—201	Prisms, alcohol	N 12.21, 12.36 P 5.79, 5.61	$C_{20}H_{14}O_{12}N_5P$	N 12.79; P 5.66	−	−	=	−

* Footnote as in Table 1. None of the substances were soluble in water, ligroin, or carbon tetrachloride.

** Yields from the action of the alcohols on the corresponding chlorides.

Acid chlorides of N-diaroxyphosphinyl-3,5-dinitroiminobenzoic acids are exceptions and are converted into alkyl esters of N-diaroxyphosphinyl-3,5-dinitroiminobenzoic acids.

$$3,5\text{-}(NO_2)_2C_6H_3C[=NPO(OAr')_2]Cl + ROH \longrightarrow HCl +$$
$$+ 3,5\text{-}(NO_2)_2C_6H_3C[=NPO(OAr')_2]OR$$

When treated with hydrogen chloride in alcohol at 20°, alkyl esters of N-diaroxy- and N-dialkoxyphosphinyliminocarboxylic acids give only diesters of aroylamidophosphoric acids.

$$ArC[=NPO(OR)_2]OAlk \xrightarrow{+HCl} AlkCl + ArCONHPO(OR)_2$$

Alkyl esters of N-dialkoxyphosphinyl-3,5-dinitroiminobenzoic acid are unchanged under the same conditions.

During alkaline hydrolysis of methyl esters of N-dimethoxyphosphinyliminocarboxylic acids there is cleavage at the C – N bond and the formation of carboxylic acids.

$$ArC[=NPO(OCH_3)_2]OCH_3 \xrightarrow[+H_2O]{+OH^-} ArCOOH$$

Under the same conditions, the methyl ester of N-dimethoxyphosphinyl-3,5-dinitroiminobenzoic acid loses only one methyl group at the phosphorus atom with the formation of the methyl ester of N-monomethoxymonohydroxyphosphinyl-3,5-dinitroiminobenzoic acid which is an isomer of the dimethyl ester of 3,5-dinitrobenzoylamidophosphoric acid.

$$3,5\text{-}(NO_2)_2C_6H_3C[=NPO(OCH_3)_2]OCH_3 \xrightarrow[+H_2O]{+OH^-}$$
$$\longrightarrow 3,5\text{-}(NO_2)_2C_6H_3C[=NPO(OCH_3)OH]OCH_3$$

It should be noted that the hydrolysis of N-diphenoxyphosphinyl-N'-arylbenzamidines and N-diphenoxyphosphinylbenzamidine in an alkaline medium proceeds analogously [6].

$$C_6H_5C[=NPO(OC_6H_5)_2]NHAr \xrightarrow[+H_2O]{+OH^-} C_6H_5C[=NPO(OC_6H_5)OH]NHAr$$

Thus, derivatives of N-phosphinyl-3,5-dinitroiminobenzoic acid differ shaprly in chemical properties from derivatives of N-phosphinyliminobenzoic acids with other substituents in the nucleus. This difference may be caused by either the high strength of 3,5-dinitrobenzoic acid in comparison with the other acids whose derivatives were investigated in this work or its structural characteristics and this problem may be solved only by further experiments.

The cleavage of acid chlorides of N-dichlorophosphinyliminocarboxylic acids by the action of alcohols to form carboxylic esters may proceed through the formation of five theoretically possible alkylation products and then through all the possible products of hydrohalogenolysis of the latter. Consequently, the intermediate products of the reaction may be:

$ArC(=NPOCl_2)OR$	(I)	$ArCONHPOCl_2$	(IA)
$ArC[=NPO(OR)Cl]Cl$	(II)	$ArC[=NPO(OH)Cl]Cl$	(IIA)
$ArC[=NPO(OR)Cl]OR$	(III)	$ArCONHPO(OR)Cl$	(IIIA)
		$ArC[=NPO(OH)Cl]OR$	(IIIB)
		$ArCONHPO(OH)Cl$	(IIIC)
$ArC[=NPO(OR)_2]Cl$	(IV)	$ArC[=NPO(OR)OH]Cl$	(IVA)
		$ArC[=NPO(OH)_2]Cl$	(IVB)
$ArC[=NPO(OR)_2]OR$	(V)	$ArCONHPO(OR)_2$	(VA)

and four more hydrohalogenolysis products (VB-VE).

Experiments showed that the action of hydrogen chloride on alkyl esters of N-dialkoxy- and N-diaroxyphosphinyliminocarboxylic acids (V) in alcohol at 20-40° and the action of alcohols on acid chlorides of N-diaroxyphosphinyliminocarboxylic acids (IV) at the boiling point form only diesters of aroylamidophosphoric acids; no further hydrohalogenolysis occurs under these conditions.

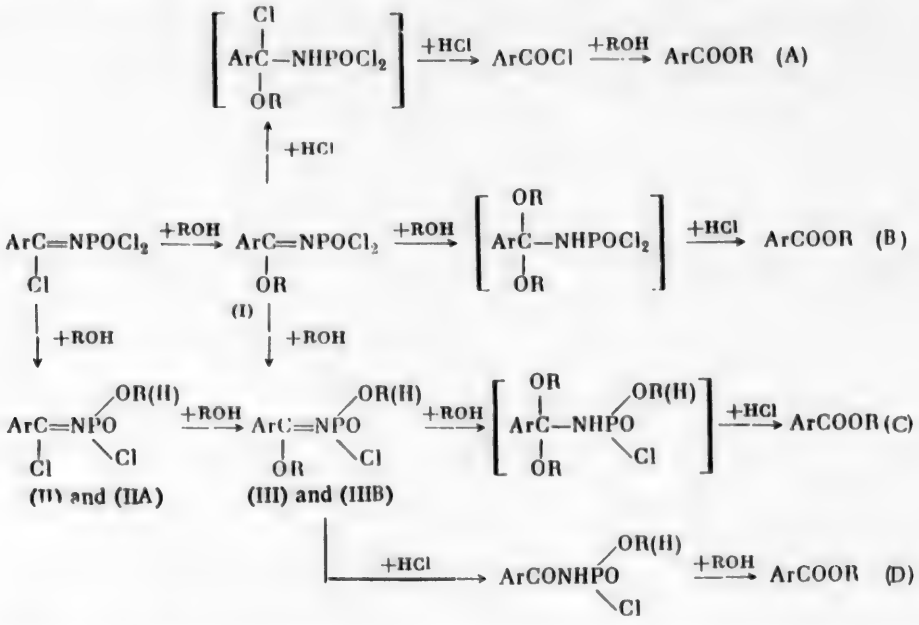
$$ArC[=NPO(OR)_2]OR + HCl \longrightarrow RCl + ArCONHPO(OR)_2$$

$$ArC[=NPO(OAr)]Cl \xrightarrow{+ROH} RCl + ArCONHPO(OAr)_2$$

Consequently, neither the alkyl esters of N-dialkoxyphosphinyliminocarboxylic acids (V), their hydrohalogenolysis products (VA-VE), including diesters of aroylamidophosphoric acids (VA), nor the acid chlorides of N-diaroxyphosphinyliminocarboxylic acids (IV) may be the intermediate products of the reaction. In addition, it was established that treatment of diacid chlorides of aroylamidophosphoric acids (IA) with alcohols gives only diesters of aroylamidophosphoric acids.

$$ArCONHPOCl_2 + 2ROH \longrightarrow 2HCl + ArCONHPO(OR)_2$$

Consequently, diacid chlorides of aroylamidophosphoric acids (IA) likewise cannot be intermediate products of the reaction and it is very improbable that the intermediates could be the compounds of analogous structure (IIIA) and (IIIC). Thus, the intermediate products of the reaction of alcohols with acid chlorides of N-dichlorophosphinyliminocarboxylic acids can only be (I), (II), and (III), the products of their indirect hydrohalogenolysis (IIA) and (IIIB), and the products of the addition of alcohols, alkoxylation, and subsequent hydrohalogenolysis.



Schemes (A) and (D) are very improbable as $ArC(NHPOCl_2)(OR)Cl$ at the moment of formation should decompose to $ArCONHPOCl_2$ and RCl and could hardly react with hydrogen chloride, while RCONHPO(OR)Cl would be converted into diesters of acylamidophosphoric acids by the action of alcohols and would not be cleaved to esters of carboxylic acids and esters of amidophosphoric acids. The last stages of schemes (A) and (D) are also improbable. Consequently, the process may proceed according to scheme (B) or (C) and scheme (B) seems more probable as in the last intermediate product of the reaction (B), the polarization of the C – N bond should be considerably greater than in the analogous product of scheme (C), which should facilitate the last stage of hydrohalogenolysis.

EXPERIMENTAL

Alkyl esters of N-dialkoxy- and N-diaroxyphosphinyliminocarboxylic acids (Tables 1 and 2). Method A. From acid chlorides of N-dichloro- and N-diaroxyphosphinyliminocarboxylic acids and sodium alcoholates. With vigorous stirring and cooling with iced water, to a solution of 0.03 or 0.01 mole of the sodium alcoholate in 20 ml of the corresponding alcohol was added a solution of 0.01 mole of the acid chloride of the N-dichloro- or N-diaroxyphosphinyliminocarboxylic acid at such a rate that the temperature of the reaction mixture remained within the range of 0 to +5° and then stirring was continued for 2 hr at 20°. The precipitated sodium chloride was removed by filtration, the filtrate evaporated in vacuum, and the residue (a viscous, oily liquid or a crystalline mass) washed carefully with water. For purification, the liquids were reprecipitated several times from benzene with ligroin and the solids were recrystallized.

Method B. From the acid chlorides of N-dichlorophosphinyliminocarboxylic acids and alcohols in the presence of triethylamine. With vigorous stirring and cooling with iced water, to a solution of 0.01 mole of the acid chloride of the N-dichloro- or N-diaroxyphosphinyliminocarboxylic acid in 30 ml of benzene was added a mixture of 0.03 or 0.01 mole of methanol, 0.03 or 0.01 mole of triethylamine, and 50 ml of benzene at such a rate that the temperature of the reaction mixture remained within the range of 0 to +5° (about 40 min). The mixture was stirred at 20° for 2 hr and left at 20° for a further 3 hr, the precipitated triethylamine hydrochloride removed, and the filtrate evaporated in vacuum. Further treatment was as in method A.

Reactions of alkyl esters of N-dialkoxy- and N-diaroxyphosphinyliminocarboxylic acids. A. With water. The esters were unchanged during prolonged stirring with water (6 hr at 20°). The esters melted when the mixture was heated. After brief boiling (10 min) and cooling, the esters crystallized and could be recovered quantitatively in an unchanged state.

B. With ammonia. Ammonia was passed into a solution of 0.002 mole of the methyl ester of dimethoxyphosphinyl-p-nitroiminobenzoic acid in 20 ml of methanol for 20 min. The temperature of the mixture first rose to 50°. The methanol was removed in vacuum to leave colorless, crystalline N-dimethoxyphosphinyl-p-nitrobenzamidine (cf. [3]), which formed needles (from alcohol) with m.p. 134-136° (90 % yield). The substance was difficultly soluble in ethanol, ether, acetone, and benzene and very difficultly soluble in ligroin and carbon tetrachloride.

Found %: N 15.50, 15.57; P 10.76. $C_9H_{12}O_5N_3P$. Calculated %: N 15.38; P 11.34.

N-Di-p-diphenoxyphosphinyl-p-chlorobenzamidine, which was synthesized previously by another method [7], was obtained analogously. The yield was 92% and the m.p. 132-134°. The product was identified by a mixed melting point.

C. Alkaline hydrolysis. A mixture of 0.01 mole of the methyl ester of dimethoxyphosphinyliminobenzoic acid, 40 ml of ethanol, and 10 ml of 2 N sodium hydroxide in water was boiled under reflux for 40 min. The ethanol and water were removed in vacuum, 5 ml of water added to the residue, and the product made acid to Congo with concentrated hydrochloric acid. The precipitated benzoic acid was collected and recrystallized (80% yield). We also hydrolyzed the methyl ester of dimethoxyphosphinyl-p-nitroiminobenzoic acid. The yield of p-nitrobenzoic acid was 90%.

D. With hydrogen chloride. A slow stream of anhydrous hydrogen chloride (1 bubble per second) was passed into a solution of 0.001 mole of the methyl ester of N-dimethoxyphosphinyliminobenzoic acid in 20 ml of methanol for 1 hr. The temperature of the mixture first rose slightly (~40°). When the hydrogen chloride had been passed in, the reaction mixture was left at 20° for 1.5 hr and then the methanol removed in vacuum. There remained the dimethyl ester of benzoylamidophosphoric acid (91% yield). The product was identified by a mixed melting point. In the same way we obtained the dimethyl ester of p-nitrobenzoylamidophosphoric acid (93% yield), the diphenyl ester of benzoylamidophosphoric acid (96% yield), and the di-p-chlorodiphenyl ester of p-chlorobenzoylamidophosphoric acid (92% yield).

Alkyl esters of N-dialkoxy- and N-diaroxyphosphinyl-3,5-dinitroiminobenzoic acids (Tables 1 and 2) could be prepared by the general methods A and B (see above), but could also be synthesized by the action of alcohols on the corresponding acid chlorides. With vigorous stirring and cooling with iced water, 0.01 mole of the acid chloride of N-dichloro- or N-diaroxyphosphinyl-3,5-dinitroiminobenzoic acid was gradually added to 15 ml of appropriate alcohol. In the case of the N-dichlorophosphinyl compounds the mixture was left at 20° for 6 hr and in the case of the N-diaroxyphosphinyl compounds, the mixture was heated to boiling and then left at 20° for 6 hr. The precipitate crystalline esters were collected, washed, and recrystallized.

Reactions of alkyl esters of N-dialkoxy- and N-diaroxyphosphinyl-3,5-dinitroiminobenzoic acid. A. With water. The esters were not changed by boiling with water.

B. Alkaline hydrolysis. A mixture of 0.001 mole of the methyl ester of N-dimethoxyphosphinyl-3,5-dinitroiminobenzoic acid, 40 ml of alcohol, and 10 ml of 2 N aqueous sodium hydroxide was gradually heated to boiling on water bath (~15 min) and boiled for 30 min. The reaction mixture was first crimson and then the color gradually disappeared. The alcohol was removed in vacuum, 5 ml of water added to the residue (a dense crystalline mass), and the mixture acidified to Congo with concentrated hydrochloric acid. The crystalline precipitate was collected, washed with water and alcohol, and dried. The yield of the methyl ester of N-monohydroxymonomethoxyphosphinyl-3,5-dinitroiminobenzoic acid was 95%; the prisms (from alcohol) had m.p. 230-231°. The ester was insoluble in water,

TABLE 3. Yields of Carboxylic Esters from the Reaction

$$ArC(=NPOCl_2)Cl \xrightarrow{+5ROH} ArCOOR$$

Ar	R	Yield %	Literature reference
C_6H_5	CH_3	74	[8]
C_6H_5	C_2H_5	73	[8]
C_6H_5	iso-C_3H_7	77	[8]
p-ClC_6H_4	CH_3	85	[9]
p-ClC_6H_4	C_2H_5	79	[10]
p-BrC_6H_4	CH_3	76	[11]
p-BrC_6H_4	C_2H_5	75	[10]
m-$NO_2C_6H_4$	CH_3	92	[13]
m-$NO_2C_6H_4$	C_2H_5	90	[14]
p-$NO_2C_6H_4$	CH_3	70	[12]
p-$NO_2C_6H_4$	C_2H_5	76	[12]

ligroin, ether, and carbon tetrachloride, sparingly soluble in alcohol and acetone, and soluble in sodium carbonate solution and dilute alkali. It was liberated unchanged on acidification of an alkaline solution. A mixed melting point with the dimethyl ester of 3,5-dinitrobenzoylamidophosphoric acid was depressed.

Found %: N 13.22, 13.28. Equiv. 1.06, 1.03. $C_9H_{10}O_8N_3P$. Calculated %: N 13.15. Equiv. 1.00.

C. With hydrogen chloride. When hydrogen chloride was passed into an alcohol solution of the methyl ester of N-dimethoxyphosphinyl-3,5-dinitroiminobenzoic acid (see above for conditions) the latter was not changed.

Cleavage of acid chlorides of N-dichlorophosphinyliminocarboxylic acids by alcohols. A 0.01 mole portion of the acid chloride of the N-dichlorophosphinyliminocarboxylic acid was added with vigorous stirring and cooling with iced water to 25 ml of the appropriate alcohol and the reaction mixture left at 20° for 6 hr. The ammonium chloride and esters of aromatic carboxylic acids formed (Table 3) were isolated by the usual methods. The liquid esters were identified by the boiling points and refractive indices and the crystalline esters by the melting points and mixed melting point. The reaction of acid chlorides of N-dichlorophosphinyliminocarboxylic acids with alcohols was also carried out in dioxane and benzene solutions; the results were the same.

The reactions of acid chlorides with N-diaroxyphosphinyliminocarboxylic acids with alcohols. A 0.001 mole portion of the acid chloride of the N-diaroxyphosphinyliminocarboxylic acid was added to 10 ml of methanol or ethanol, the mixture heated to boiling and then left at 20° for 6 hr, and the solvent removed in vacuum. The residual diester of an aroylamidophosphoric acid was recrystallized from alcohol. It was identified by a mixed melting point. We obtained the diphenyl ester of benzoylamidophosphoric acid (85% yield), the diphenyl ester of p-chlorobenzoylamidophosphoric acid (90% yield), and the di-p-chlorodiphenyl ester of p-chlorobenzoylamidophosphoric acid (84% yield).

Alcoholysis of diacid chlorides of aroylamidophosphoric acids. A 0.01 mole portion of the diacid chloride of the aroylamidophosphoric acid was added to 10 ml of methanol, the mixture heated to boiling and then kept at 20° for 24 hr, and the precipitated crystalline dimethyl esters of aroylamidophosphoric acids collected and recrystallized. The esters were identified by mixed melting points. We obtained the dimethyl esters of benzoylamidophosphoric (83%), m-nitrobenzoylamidophosphoric (90%), p-nitrobenzoylamidophosphoric (95%), and 3,5-dinitrobenzoylamidophosphoric (97%) acids.

SUMMARY

1. The action of alcoholates or alcohols in the presence of tertiary bases on acid chlorides of N-dichloro- and N-diaroxyphosphinyliminocarboxylic acids forms esters of N-dialkoxy- and N-diaroxyphosphinyliminocarboxylic acids.

2. The action of ammonia on esters of N-dialkoxy- and N-diaroxyphosphinyliminocarboxylic acids yields N-dialkoxy- and N-diaroxyphosphinylareneamidines.

3. When acid chlorides of N-dichlorophosphinyliminocarboxylic acids are treated with alcohols in the absence of bases, there is cleavage of the former to yield esters of carboxylic acids, ammonium chloride, alkyl halides, and water-soluble phosphoric acid derivatives. Cleavage of the molecule (hydrohalogenolysis) occurs at the stage of one of the first or second intermediate products of alkoxylation of the starting acid chlorides. An exception is the acid chloride of N-dichlorophosphinyl-3,5-dinitroiminobenzoic acid, which reacts with alcohols both in the presence and in the absence of bases to give only esters of N-dialkoxyphosphinyl-3,5-dinitroiminobenzoic acid.

4. Esters of N-dialkoxy- and N-diaroxyphosphinyl-3,5-dinitroiminobenzoic acid differ sharply in chemical properties from esters of N-dialkoxy- and N-diaroxyphosphinyliminocarboxylic acids with other substituents in the nucleus.

5. On treatment with alcohols, acid chlorides of N-diaroxyphosphinyliminocarboxylic acids give diaryl esters of aroylamidophosphoric acids. Under the same conditions, derivatives of 3,5-dinitrobenzoic acid give esters of N-diaroxyphosphinyl-3,5-dinitroiminobenzoic acid.

6. Esters of N-dialkoxy- and N-aroxyphosphinyliminocarboxylic acids are converted by hydrohalogenolysis into diesters of aroylamidophosphoric acids. Derivatives of 3,5-dinitroiminobenzoic acid are not changed under the same conditions.

7. During alkaline hydrolysis, esters of N-dimethoxyphosphinyliminocarboxylic acids are cleaved to form carboxylic acids. Under the same conditions, the corresponding derivatives of 3,5-dinitrobenzoic acid are converted into esters of N-monomethoxymonohydroxyphosphinyl-3,5-dinitroiminobenzoic acid.

8. When treated with alcohols, diacid chlorides of aroylamidophosphoric acids give diesters of aroylamidophosphoric acids.

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BISTRIETHYLENETRIAMIDOPHOSPHAZO DERIVATIVES OF DIBASIC ACIDS AND DIETHYLENEDIAMIDES OF BIS-N-DIETHYLENEDIAMIDOPHOSPHINYLIMINOCARBOXYLIC ACIDS

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By the action of ethylenimide on bistrichlorophosphazo derivatives of dibasic acids [1] and diacid chlorides of bis-N-dichlorophosphinyliminocarboxylic acids [2] we prepared bistriethylenetriamidophosphazo derivatives of five dibasic acids and diethylenediamides of two bis-N-diethylenediamidophosphinyliminocarboxylic acids (cf. [3]) for studying their antiblastic properties.

$$Ac(N{=}PCl_3)_2 \xrightarrow[+6N(C_2H_5)_3]{+6HNC_2H_4} Ac[N{=}P(NC_2H_4)_3]_2,$$

$$Ac = \underset{(I)}{m\text{-and}}\ \underset{(II)}{p\text{-}}C_6H_4(CO)_2;\quad \underset{(III)}{m\text{-and}}\ \underset{(IV)}{p\text{-}}C_6H_4(SO_2)_2;\quad \underset{(V)}{SO_2}.$$

$$ArC(=NPOCl_2)Cl \xrightarrow[+6N(C_2H_5)_3]{+6HNC_2H_4} ArCl{=}NPO(NC_2H_4)_2]NC_2H_4,$$

$$Ar = \underset{(VI)}{m\text{-and}}\ \underset{(VII)}{p\text{-}}C_6H_4.$$

The study of the antiblastic properties of these ethyleneamides is of interest as phosphoric acid derivatives with six ethyleneamide groups in the molecule were unknown up to now.

The bistriethylenetriamidophosphazo derivatives of dibasic acids and diethylenediamides of bis-N-diethylenediamidophosphinyliminocarboxylic acids (Table 1) were colorless crystalline substances [with the exception of the liquid (VI)], which were weakly basic and readily polymerized by the action of dilute mineral acids. The substances (I) and (II) were polymerized particularly readily by prolonged storage (three months) or by boiling their neutral aqueous solutions. Substances (I), (V) and (VII) were soluble in water and did not change in aqueous solutions when kept for a long time at 20°. All the other substances were difficutly soluble in water. When compounds (I) and (II) were heated rapidly in a capillary, they melted sharply over a range of two degrees; when heated slowly, they darkened gradually and decomposed at 170-180° with an explosion to form a black carbonaceous residue with a repulsive odor of phosphine. For identification, the liquid (VI) was converted into the crystalline hexapicrate, which was insoluble in water and the usual organic solvents. It was not possible to obtaine hexaethylenehexaamides from p-trichlorophosphazosulfonyltrichlorophosphazobenzoyl

$$(p\text{-}Cl_3P = NSO_2C_6H_4CON = PCl_3),$$

o-trichlorophosphazosulfonyltrichlorophosphazophenyl ($o\text{-}Cl_3P = NC_6H_4SO_2N = PCl_3$), or trichlorophosphazo-N-arylsulfonyliminoaroyls

$$[ArC(= NSO_2Ar)N = PCl_3]\ [4]$$

When the reaction was carried out under the most varied conditions, we only isolated high melting polymeric products, which were insoluble in the usual organic solvents.

TABLE 1. Bistriethylenetriamidophosphazo Derivatives of Dibasic Acids of the Type Ac[N = P(NC$_2$H$_4$)$_3$]$_2$ and Diethylenediamides of Bis-N-Diethylenediamidophosphinyliminocarboxylic Acids of the Type Ar[C(=NPO(NC$_2$H$_4$)$_2$)NC$_2$H$_4$]$_2$

Substance	Ac	Yield %	Melting point	Recrystallization solvent	Found (%)	Empirical formula	Calculated (%)	Solubility*			
								water	ethanol	benzene	acetone
(I)	m-C$_6$H$_4$(CO)$_2$	62	130–132°*	Benzene	23.55	C$_{20}$H$_{28}$O$_2$N$_8$P$_2$	23.62	+	+	+	+
(II)	p-C$_6$H$_4$(CO)$_2$	50	136–138*	Benzene	23.50	C$_{20}$H$_{28}$O$_2$N$_8$P$_2$	23.62	−	−	+	+
(III)	m-C$_6$H$_4$(SO$_2$)$_2$	51	130–132	Chloroform	19.71	C$_{18}$H$_{28}$O$_4$N$_8$S$_2$P$_2$	20.51	=	−	−	−
(IV)	p-C$_6$H$_4$(SO$_2$)$_2$	57	175 (decomp.)	Chloroform	19.86	C$_{18}$H$_{28}$O$_4$N$_8$S$_2$P$_2$	20.51	=	−	−	−
(V)	SO$_2$	61	94–95	Benzene	27.48	C$_{12}$H$_{24}$O$_2$N$_8$SP	27.58	+	+	+	+
(VI)	m-C$_6$H$_4$ (Ar)	69	Liquid		—	C$_{20}$H$_{28}$O$_2$N$_8$P$_2$	—	=	+	+	+
(VII)	p-C$_6$H$_4$ (Ar)	47	108–109	Acetone	23.51	C$_{20}$H$_{28}$O$_2$N$_8$P$_2$	23.62	+	+	−	+

* With slow heating it gradually darkened and decomposed rapidly at 170-180°.

** +) Soluble; −) difficultly soluble; =) insoluble. All the substances were soluble in chloroform and insoluble in ether and ligroin.

As starting materials we prepared two bisphosphazo compounds and the diacid chloride of bis-N-dichlorophosphinyldiiminoterephthalic acid which have not been described in the literature (Table 2).

EXPERIMENTAL

Bistriethylenetriamidophosphazoisophthaloyl (I). With stirring and cooling to a mixture of 0.06 mole of ethyleneimine, 0.06 mole of triethylamine, and 10 ml of benzene was added a solution of 0.005 mole of bistrichlorophosphazoisophthaloyl in 300 ml of benzene at such a rate that the temperature of the mixture remained within the range of 20-25° and stirring was continued for a further 2 hr. The precipitate of triethylamine hydrochloride was removed and washed with benzene. The benzene was distilled from the filtrate in vacuum at 30°. The colorless, crystalline residue of (I) was collected, washed with benzene, and recrystallized.

We also prepared (II) in this way. In the preparation of substances (III), (IV), (V), and (VII), the reaction and subsequent stirring for 2 hr were carried out at 5-8°. If the reaction was carried out at a higher temperature, the yields were reduced appreciably and a considerable amount of polymeric products was formed. The substances (III) and (IV) were difficultly soluble in benzene and therefore precipitated together with triethylamine hydrochloride. The precipitate was collected, washed successively with water, alcohol, and ether, and recrystallized. Substance (V) was isolated analogously to (I). In the case of (VII), after the removal of benzene in vacuum, 5 ml of acetone was added to the crystalline residue, the mixture stirred, and the crystalline product collected, washed with acetone, and recrystallized. Substance (VI) was synthesized at 15-20°. Removal of the benzene in vacuum left an oily, light yellow liquid, which did not distill in vacuum without decomposition. Substance (VI) was converted into the hexapicrate for identification. To a solution of 0.002 mole of the liquid (VI) in 100 ml of benzene was added a solution of 0.012 mole of picric acid in 100 ml of benzene. The precipitate was collected and washed with benzene. The hexapicrate of the diethyldiamide of bis-N-diethylenediamidophosphinyldiiminoisophthalic acid was a finely crystalline yellow powder with m.p. 191-192° (with decomp.); it was insoluble in water and the usual organic solvents.

Found %: N 19.33. $C_{56}H_{85}O_{44}N_{26}P_2$. Calculated %: N 19.66.

Action of hydrochloric acid on bistriethylenetriamidophosphazoterephthaloyl (II). To a solution of 0.0005 mole of (II) in 10 ml of alcohol was added 2 ml of 0.3 N aqueous hydrochloric acid and the mixture heated for 30 min. A colorless precipitate began to form immediately and the amount of it gradually increased.

TABLE 2

Formula*	Yield %	M. p.	Found		Empirical formula	Cl found (%)**
			Cl (%)	equivalent after hydrolysis		
p-$C_6H_4(CON{=}PCl_3)_2$	92	118—120°	49.07	9.96	$C_8H_4O_2N_2P_2Cl_6$	48.90
p-$Cl_3P{=}NSO_2C_6H_4CON{=}{=}PCl_3$	65	72—75	49.10	10.10 9.90	$C_7H_4O_3N_2P_2SCl_6$	48.93
p-$C_6H_4[C(=NPOCl_2)Cl]_2$	100	118—120***	48.35 48.02	—	$C_8H_4O_2N_2P_2Cl_6$	48.90

* All the substances were readily soluble in acetone and benzene, more difficultly soluble in ether and carbon tetrachloride, and insoluble in ligroin. All the substances crystallized as colorless prisms from a mixture of benzene and ligroin.

** Calculated: equivalent after hydrolysis 10.0.

*** It melted at 82-85° after storage at 20° for a day.

The precipitate was collected, washed with alcohol, and dried in air. The yield was 45%. The product consisted of glassy scales, which were insoluble in the usual organic solvents and had m.p. 200-250° (with decomp.). The same polymer was obtained when aqueous alcohol solutions of (II) containing hydrochloric acid were kept for a long time at room temperature.

Bistrichlorophosphazoterephthaloyl (Table 2). A mixture of 0.03 mole of the diamide of terephthalic acid, 0.062 mole of phosphorus pentachloride, and 85 ml of carbon tetrachloride was boiled under reflux until the evolution of hydrogen chloride ceased (2-3 hr). The carbon tetrachloride was removed in vacuum and the solid residue recrystallized.

p-Trichlorophosphazosulfonyltrichlorophosphazobenzoyl (Table 2). A mixture of 0.02 mole of p-sulfamidobenzamide, 0.041 mole of phosphorus pentachloride, and 70 ml of toluene was heated on an oil bath at 90-100° until the evolution of hydrogen chloride ceased completely (2-2.5 hr). The solvent was removed in vacuum. The residue was a dense crystalline mass, which was ground up, washed with ligroin, and recrystallized.

Diacid chloride of bis-N-dichlorophosphinyldiiminoterephthalic acid (Table 2). A mixture of 0.01 mole of the bis-N-dichlorophosphinyldiamide of terephthalic acid and 0.021 mole of phosphorus pentachloride was heated on an oil bath at 130-150° until the evolution of hydrogen chloride ceased completely (40-50 min). The phosphorus oxychloride was removed in vacuum. There remained a thick viscous liquid, which gradually crystallized on treatment with ligroin. The crystals were collected, washed with ligroin, and recrystallized.

SUMMARY

The action of ethylenimine on bistrichlorophosphazo derivatives of dibasic acids and diacid chlorides of bis-N-dichlorophosphinyliminocarboxylic acids formed bistriethylenetriamidophosphazo derivatives of dibasic acids and diethylenediamides of bis-N-diethyleneamidophosphinyliminocarboxylic acids.

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REACTIONS OF HYDROXYMETHYLPHOSPHINIC ESTERS WITH DIMETHYLTHIOCARBAMYL CHLORIDE AND ARYL ISOTHIOCYANATES

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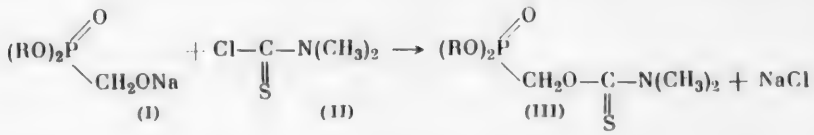
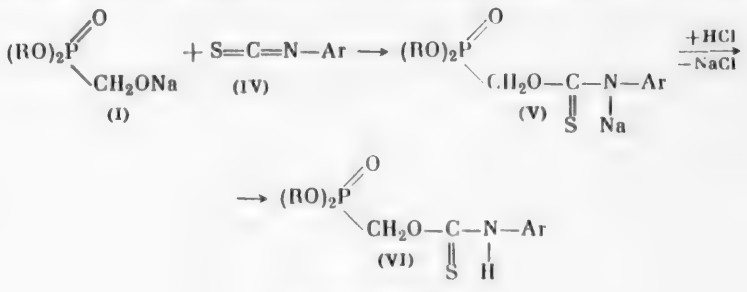
Dialkyl esters of α-hydroxyphosphinic acids, which were prepared by V. S. Abramov [1, 2], have a high reactivity [3, 4] and may be used for the synthesis of a variety of their derivatives. In studying the reaction of dialkylthiocarbamyl chlorides and aryl isothiocyanates with dialkylphosphorous acids [5, 6], we also considered it interesting to investigate their behavior toward dialkyl esters of hydroxymethylphosphinic acid [in the form of the sodium derivatives (I)]. In the case of dimethylthiocarbamyl chloride (II), the reaction may be represented by the following equation:



The reaction proceeds very vigorously with heat evolution. It yields the dimethylthiocarbamic esters of dialkyl esters of hydroxymethylphosphinic acid (III), which are given in Table 1. They are all yellow oils, which were purified by molecular distillation.

Aryl isothiocyanates (IV) and compound (I) react (in ether solution) very vigorously with heat evolution to form arylthiocarbamic esters of dialkyl esters of hydroxymethylphosphinic acid (VI) according to the scheme:



Ar = C_6H_5, $C_6H_4OCH_3$.

The compounds (VI) were colorless or slightly yellow crystalline substances, which dissolved very readily in ether and very sparingly in hydrocarbons (n-hexane and n-octane), which we used to purify them. The properties of these compounds are given in Table 2. In addition to solids, in individual cases (with the radicals R and Ar equal to n-C_4H_9 and C_6H_5, iso-C_5H_{11} and C_6H_5, and C_2H_5 and $C_6H_4OCH_3$) we obtained compounds (VI) as yellow, glycerol-like oils, which we have not been able to distil as yet, and therefore they are not given in Table 2.

We also established that (I) reacts with p-nitrophenyl and phenyl isothiocyanates. These reactions are being studied at the present time.

In the preparation of compounds (VI), we sometimes observed the precipitation from ether solution of the intermediate reaction product (V). In particular, we isolated the sodium derivative of compound 4 (Table 2) as a color-

TABLE 1. Dimethylthiocarbamic Esters of Dialkyl Esters of Hydroxymethylphosphinic Acid

$$(RO)_2P(=O)-CH_2-O-C(=S)-N(CH_3)_2$$

R	Yield %	Glycerol bath temperature	Pressure (mm)	n_D^{20}	d_4^{20}	MR, found	MR, calculated	Found % N	Empirical formula	Calculated % N
C_2H_5*	72.0	86—87°	0.008—0.004	1.4932	1.1600	63.98	64.03	5.91, 5.92	$C_8H_{18}O_4NSP$	5.71
n.-C_3H_7	68.8	89—93	0.0008	1.4861	1.1057	73.59	73.26	4.68, 4.84	$C_{10}H_{22}O_4NSP$	4.94
iso-C_3H_7**	79.7	68—73	0.0008—0.0004	1.4837	1.1013	73.54	73.26	5.19, 5.31	$C_{10}H_{22}O_4NSP$	4.94
n.-C_4H_9	45.2	108—110	0.003—0.002	1.4847	1.0769	82.82	82.50	4.65, 4.45	$C_{12}H_{26}O_4NSP$	4.53
iso-C_4H_9	74.6	86—89	0.0006—0.0004	1.4827	1.0750	82.67	82.50	4.65, 4.80	$C_{12}H_{26}O_4NSP$	4.53

* Found %: S 12.86, 13.03. Calculated %: S 13.05.

** Found %: S 11.64, 12.12. Calculated %: S 11.30.

less, finely crystalline substance, which could be stored well in absolute ether, but rapidly deliquesced in contact with moist air. It dissolved readily in water with hydrolysis (as was indicated by the strong alkaline reaction of the solution).

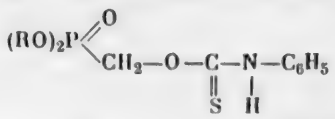
EXPERIMENTAL

Sodium derivative of dialkyl ester of hydroxymethylphosphinic acid. The reaction was carried out in a four-necked flask, fitted with a stirrer with a seal (fitted on the reflux condenser), a thermometer, a dropping funnel, and a reflux condenser, protected with calcium-chloride tubes. Into the flask were placed 50 ml of absolute ether and 2.3 g of finely cut metallic sodium, the dialkylphosphorous acid (0.1 mole) was added dropwise, and the sodium dissolved completely, finally with stirring and heating. At the end of the reaction, the solution was allowed to cool, 3 g (0.1 mole) of paraformaldehyde rapidly introduced with the dropping funnel removed from the neck of the flask, and then the dropping funnel replaced. A vigorous reaction was observed and the ether boiled. The paraformaldehyde reacted completely. The substance (I) formed either remained in solution or formed a massive white precipitate, which trapped the whole of the solvent. The substance obtained was allowed to cool and used in the same apparatus for subsequent syntheses.

Reaction of (I) with dimethylthiocarbamyl chloride. A solution of 0.1 mole of dimethylthiocarbamyl chloride (II) in 30 ml of absolute ether was added dropwise with stirring over a period of 10-15 min to substance (I). There was strong heat evolution and the ether boiled. The reaction mixture was heated for 30 min to complete the process. To precipitate the colloidal sodium chloride formed, 1 ml of water was added to the reaction mixture, which was left for from 2-3 to 12 hr. The ether solution was filtered. The filtrate was washed twice (30 ml portions) with water to remove sodium chloride residues, and dried and the ether removed. For the removal of the remaining ether, the yellow oils obtained were kept at 1-10 mm with a bath temperature of 30-40° for a long time. The condensation products were then subjected to molecular distillation.

Reaction of (I) with aryl isothiocyanates. The aryl isothiocyanate (0.1 mole) was added dropwise with stirring to substance (I). Heat was evolved (vigorous boiling of the ether) and after a few minutes, the reaction mixture either crystallized or changed into a yellow, glycerol-like liquid. The reaction mixture was heated for 30 min to complete the reaction, allowed to cool and transferred to a separatory funnel and 30 ml of dilute hydrochloric acid (0.1 mole) slowly added. After the mixture had been shaken, the aqueous layer was separated and the ether solution washed 2-4 times with water (20-30 ml portions) and dried. To the ether solution was added n-octane or n-hexane to precipitate a yellow oil, which gradually crystallized in the case of the substances given in Table 2. The solids were puri-

TABLE 2. Arylthiocarbamic Esters of Dialkyl Esters of Hydroxymethylphosphinic Acid



Sample No.	R	Yield %	M. p.	Recrystallization solvent	Found % N	Empirical formula	Calculated % N
1	C_2H_5*	56.7	75.0—75.7°	Ether–n-octane	4.76, 5.01	$C_{12}H_{18}O_4NSP$	4.61
2	n.-C_3H_7	36.4	50.8—52.3	Ether–n-octane	4.05, 3.69	$C_{14}H_{22}O_4NSP$	4.23
3	iso -C_3H_7	55.9	97.2—97.9	Ether	4.34, 4.36	$C_{14}H_{22}O_4NSP$	4.23
4	iso C_4H_9	45.1	70.0—71.2	Ether–n-hexane	4.37, 4.30	$C_{16}H_{26}O_4NSP$	3.89

* Found %: P 10.32, 10.64. Calculated %: P 10.21.

fied by repeated reprecipitation from ether with n-octane or n-hexane. The oily products were washed with a mixture of ether and n-hexane.

SUMMARY

1. Condensation of the sodium derivatives of dialkyl esters of hydroxymethylphosphinic acid with dimethylthiocarbamyl chloride yielded dimethylthiocarbamic esters of dialkyl esters of hydroxymethylphosphinic acid, which have not been described in the literature previously.

2. By the reaction of sodium derivatives of dialkyl esters of hydroxymethylphosphinic acid with aryl isothiocyanates, we synthesized arylthiocarbamic esters of dialkyl esters of hydroxymethylphosphinic acid, which were previously unknown.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

SYNTHESES WITH FREE HYDROXYL RADICALS

II. REACTIONS OF ALIPHATIC ESTERS WITH HYDROXYL RADICALS

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We have already reported [1] that by reacting with hydroxyl radicals in an aqueous medium at room temperature, aliphatic esters undergo dehydrodimerization with the formation of the corresponding diesters.

In the present work we studied the reaction of methyl isobutyrate and n-butyrate, ethyl propionate, dimethyl adipate, and n-butyl acetate with hydroxyl radicals.

The products from the reaction of methyl isobutyrate were the dimethyl esters of α,α'-dimethyladipic, α,α,α'-trimethylglutaric, and tetramethylsuccinic acids (yields of 12, 14.6, and 2% respectively), a trimer (12.6%), a tetramer (15.2%), acetone, and isobutyric acid (Table 1). Hydrolysis of the dimers yielded meso- α,α'-dimethyladipic and α,α,α'-trimethylglutaric acids, respectively.

From the products from the reaction of methyl n-butyrate with hydroxyl radicals we isolated dimethyl suberate, a trimer, a tetramer, propionaldehyde, and n-butyric acid (Table 2).

From the products from the reaction of ethyl propionate with hydroxyl radicals we isolated the mono- and diethyl esters of adipic acid (Table 3). No ligomeric products obtained in this synthesis were isolated.

Dimethyl adipate yielded an unidentified dimer (17% yield) and monomethyl adipate.

The dimer formed by the reaction of butyl acetate with hydroxyl radicals was an individual product, which yielded a glycol on hydrolysis. When the glycol was passed over alumina at 270°, one molecule of water was eliminated smoothly to give an almost quantiative yield of the dehydration product. The infrared spectrum* of the latter (Fig. 1) did not contain absorption bands characteristic of a double bond >C = C< or a hydroxyl group (absorption maxima at 5.95-6.18 and 2.90-3.13 μ, respectively [2]), but had an absorption band with a maximum at 9.2 μ, which is characteristic of the tetrahydrofuran ring [2]. In this case, a quantitative yield of a substituted tetrahydrofuran was possible only if the substance was 2,3-diethylbutane-1,4-diol.

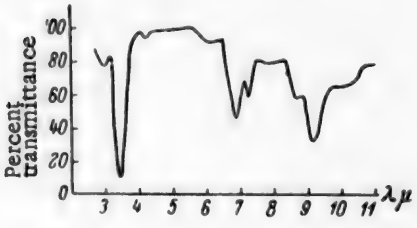

Fig. 1. Infrared spectrum of dehydration product.

$$\begin{matrix} C_2H_5CHCH_2OH \\ | \\ C_2H_5CHCH_2OH \end{matrix} \xrightarrow[270^\circ]{Al_2O_3} \begin{matrix} C_2H_5CHCH_2 \\ | \\ C_2H_5CHCH_2 \end{matrix}\!\!>\!O + H_2O.$$

2,3-Diethylbutane-1,4-diol has been mentioned in the literature [3, 4], but its physical constants were not given.

On the basis of the above account and with allowance for all the reaction products (Tables 1-3), it is possible to draw up a scheme for the reaction of aliphatic esters with hydroxyl radicals. It is given for the case of methyl isobutyrate.

Hydroxyl radicals attack the C – H bonds of the ester molecule, abstract hydrogen, and form organic free radicals:

$$1)\quad CH_3CH(CH_3)COOCH_3 + \cdot OH \rightarrow \begin{cases} \dot{C}H_2CH(CH_3)COOCH_3 \\ CH_3\dot{C}(CH_3)COOCH_3 \\ CH_3CH(CH_3)COOCH_2 \end{cases}$$

* The infrared spectra were plotted on a double-beam IKS-14 instrument with a sodium chloride prism.

TABLE 1. Reaction of Methyl Isobutyrate with Hydroxyl Radicals

Substances	Amounts			Moles of ester converted per mole of H_2O_2
	grams	moles	moles per mole of H_2O_2	
Reagents				
Hydrogen peroxide	22.6	0.666	–	–
Starting methyl isobutyrate	204	2.00	3.00	–
Unreacted methyl isobutyrate	133	1.30	1.95	–
Methyl isobutyrate reacting and losses	71	0.70	1.05	–
Products				
Dimers	19.2	0.095	0.143	0.286
Trimer	9.1	0.030	0.045	0.135
Tetramer	10.3	0.026	0.038	0.152
Monomethyl ester of dicarboxylic acid with 8 C atoms	1.2	0.006	0.010	0.021
Acetone	0.65	0.011	0.016	0.016
Isobutyric acid	12.0	0.137	0.206	0.206
			Total	0.816

TABLE 2. Reaction of Methyl Butyrate with Hydroxyl Radicals

Substances	Amounts		moles of ester converted per mole of H_2O_2
	moles	moles per mole of H_2O_2	
Reagents			
Hydrogen peroxide	0.666	–	–
Starting methyl butyrate	2.00	3.00	–
Unreacted methyl butyrate	1.37	2.06	–
Methyl butyrate reacting and losses	0.63	0.94	–
Products			
Dimers	0.815	0.122	0.224
Trimer	0.011	0.017	0.052
Tetramer	0.010	0.015	0.060
Monomethyl ester of dicarboxylic acid with 8 C atoms	0.008	0.012	0.022
Propionaldehyde	0.0048	0.007	0.011
n-Butyric acid	0.170	0.255	0.255
		Total	0.644

TABLE 3. Reaction of Ethyl Propionate with Hydroxyl Radicals

Substances	Amounts		
	moles	moles per mole of H_2O_2	moles of ester converted per mole of H_2O_2
Reagents			
Hydrogen peroxide	0.666	–	–
Starting ethyl propionate	2.00	3.00	–
Unreacted ethyl propionate	1.18	1.77	–
Ethyl propionate reacting and losses	0.82	1.23	–
Products			
Dimers	0.031	0.046	0.093
Monomethyl ester of acid with 6 C atoms	0.067	0.101	0.172
Oligomers	–	–	0.050
Acetaldehyde	–	–	–
Propionic acid	0.41	0.615	0.615
		Total	0.930

The radicals obtained as a result of abstraction of α-hydrogen atoms then give oxidation products.

2) $CH_3\dot{C}(CH_3)COOCH_3 + \cdot OH \longrightarrow CH_3C(OH)(CH_3)COOCH_3 \longrightarrow CH_3CCH_3 + HCOOCH_3$ (O above the C)

3) $CH_3\dot{C}HCOOCH_3 + \cdot OH \longrightarrow CH_3CH(CH_3)COOCH_2OH \longrightarrow CH_3CH(CH_3)COOH + H_2CO.$

Radicals formed by abstraction of hydrogen atoms remote from the functional group and stabilized α-radicals dimerize:

4) $2\dot{C}H_2CH(CH_3)COOCH_3 \longrightarrow \begin{matrix} CH_2CH(CH_3)COOCH_3 \\ | \\ CH_2CH(CH_3)COOCH_3 \end{matrix}$ (A)

5) $\dot{C}H_2CH(CH_3)COOCH_3 + CH_3\dot{C}(CH_3)COOCH_3 \longrightarrow \begin{matrix} CH_2CH(CH_3)COOCH_3 \\ | \\ C(CH_3)_2COOCH_3 \end{matrix}$

6) $2CH_3\dot{C}(CH_3)COOCH_3 \longrightarrow \begin{matrix} (CH_3)_2CCOOCH_3 \\ | \\ (CH_3)_2CCOOCH_3. \end{matrix}$

Dimer molecules are also attacked by hydroxyl radicals:*

7) $A + \cdot OH \longrightarrow \begin{matrix} \dot{C}HCH(CH_3)COOCH_3 \\ | \\ CH_2CH(CH_3)COOCH_3 \end{matrix}$ (B) $+ H_2O$

$A + \cdot OH \longrightarrow \begin{matrix} CH_2CH(CH_3)COOCH_3 \\ | \\ CH_2\dot{C}H(CH_3)COOCH_2 \end{matrix}$ (C) $+ H_2O$

* We do not give all the possible radicals from the dimers here, but only the scheme for one of the possible variants.

8) $CH_2CH(CH_3)COOCH_3 + B \rightarrow$ trimer

9) $2B \rightarrow$ tetramer

10) $C + \cdot OH \rightarrow \begin{matrix} CH_2CH(CH_3)COOCH_3 \\ | \\ CH_2CH(CH_3)COOCH_2OH \end{matrix} \rightarrow$

$$\rightarrow \begin{matrix} CH_2CH(CH_3)COOCH_3 \\ | \\ CH_2CH(CH_3)COOH \end{matrix} + H_2CO.$$

EXPERIMENTAL

Experimental procedure. Into a 2.5 liter flask, fitted with a stirrer, two calibrated dropping funnels, and a thermometer, were placed 2 moles of the ester, 1 liter of water, and 25 ml of concentrated sulfuric acid. With the reactor cooled with iced water and the reaction mixture stirred, equivalent amounts of an aqueous solution of hydrogen peroxide (0.66 mole in 100 ml of solution) and a sulfuric acid solution of ferrous sulfate (0.66 mole of $FeSO_4 \cdot 7H_2O$, 0.66 mole of H_2SO_4, and 400 ml of water) were run simultaneously into flask over a period of 10 min. The temperature of the reaction mixture thereupon rose from 5 to 25°. Stirring was continued for a further 10 min. After the stirring, the organic and aqueous layers were separated. The organic layer was dried with magnesium sulfate.

Reaction of esters with hydroxyl radicals. Methyl isobutyrate. The organic layer (175 g) was distilled. Distillation of the monomer (133 g, n^{20}_D 1.3840) left 42 g of a viscous liquid (n^{20}_D 1.4400). The latter was vacuum distilled. The distillation curve is shown in Fig. 2. The 1st and 2nd fractions* were neutralized with sodium carbonate and steam distilled. We isolated dimethyl tetramethylsuccinate with m.p. 30-31° (m.p. 31° [5]).

Found %: C 58.98; H 8.90. M 202.** $C_{10}H_{18}O_4$. Calculated %: C 59.38; H 8.97.

Fractions 3-6 (18 g, b.p. 105-118° at 15 mm, n^{20}_D 1.4318) were fractionated on a column of 25 theoretical plates. We obtained approximately equal amounts of fraction 1', which boiled at 90° (11 mm) (n^{20}_D 1.4328, d_4^{20} 1.0305), and fraction 2', which boiled at 102-103° (11 mm) (n^{20}_D 1.4295, d_4^{20} 1.0174).

Fraction 1'.

Found %: C 59.57; H 8.90. M 210; MR_D 50.99. $C_{10}H_{18}O_4$. Calculated %: C 59.38; H 8.97. M 202; MR_D 51.69.

A mixture of 10 g of fraction 1', 285 ml of water, and 5 ml of concentrated sulfuric acid was boiled for 26 hr with stirring by a magnetic stirrer. The water was then removed in vacuum to a residual volume of about 50 ml. The precipitated crystals (2.8 g) were recrystallized once from water, when they had m.p. 97-98° (α,α,α'-trimethylglutaric acid has m.p. 97-98° [5]).

Found %: C 55.45; H 8.18. Equiv. 86.9. $C_8H_{14}O_4$. Calculated %: C 55.16; H 8.10. Equiv. 87.1.

Fraction 2'.

Found %: C 59.12; H 8.79. M 212; MR_D 51.30. $C_{10}H_{10}O_4$. Calculated %: C 59.38; H 8.97. M 202; MR_D 51.69.

A 10 g sample of fraction 2' was hydrolyzed analogously to fraction 1' for 13 hr. After evaporation and cooling, there precipitated 4.3 g of crystals, which melted at 140° after 5 recrystallizations from water (meso-α,α'-dimethyladipic acid has m.p. 140-141° [5]).

Found %: C 55.38; H 7.97. Equiv. 88.3. $C_8H_{14}O_4$. Calculated %: C 55.16; H 8.10. Equiv. 87.1.

Thus, fraction 1' was dimethyl α,α,α'-trimethylglutarate and fraction 2' was dimethyl α,α'-dimethyladipate (dimethyl α,α'-dimethyladipate has n^{20}_D 1.4295 [6]). Fraction 8 (9.8 g, n^{20}_D 1.4516, acidity calculated on monomethyl ester of a dicarboxylic acid with 8 C atoms, 7%***) was dissolved in diethyl ether and neutralized with sodium bicarbonate. Drying and distillation yielded 6.5 g of a neutral trimer of methyl isobutyrate (a colorless, oily liquid with b.p. 142-148° at 3 mm, n^{20}_D 1.4522, d_{20}^{20} 1.0798).

Found %: C 59.82; H 8.53. M 313; MR_D 75.32. $C_{15}H_{26}O_5$. Calculated %: C 59.59; H 8.67. M 302; MR_D 76.43.

* The first fractions contained some isobutyric acid.

** Determined cryoscopically in benzene in this and later cases.

*** As will be shown below, the reaction of dimethyl adipate with hydroxyl radicals yields considerable amounts of monomethyl adipate. In the given case, therefore, the acidity was ascribed to the monoester.

Fraction 10 (11 g, n^{20}_D 1.4634, acidity 6.5%) was neutralized as described above. We obtained 6 g of a tetramer of methyl isobutyrate (a very viscous liquid, boiling with slight decomposition at 200-220° at 2 mm, n^{20}_D 1.4650, d_{20}^{20} 1.120).

Found %: C 59.36; H 8.40. M 426; MR_D 99.60. $C_{20}H_{34}O_8$. Calculated %: C 59.68; H 8.51. M 402; MR_D 101.18.

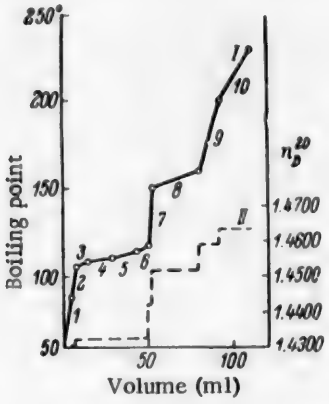

Fig. 2. Distillation curve of dimers and oligomers from methyl isobutyrate at a pressure of 15 mm Hg. I) Boiling point; II) refractive index.

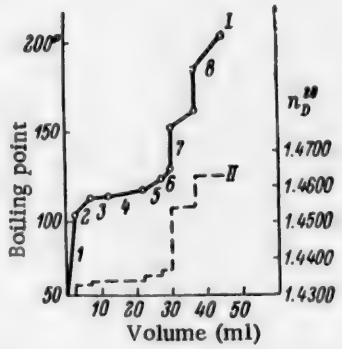

Fig. 3. Distillation curve of dimers and oligomers from methyl butyrate. I) Boiling point; II) refractive index.

An aliquot part of the aqueous layer was fractionated. The aqueous distillates were collected until a test with a saturated hydrochloric acid solution of 2,4-dinitrophenylhydrazine no longer gave a precipitate. We isolated acetone 2,4-dinitrophenylhydrazone with m.p. 123-124° (from alcohol). A mixed melting point with authentic acetone 2,4-dinitrophenylhydrazone was not depressed.

Found %: C 45.38; H 4.19. $C_9H_{10}O_4N_4$. Calculated %: C 45.59; H 4.35.

An aliquot part of the aqueous layer was extracted repeatedly with diethyl ether. Drying and distillation yielded isobutyric acid (n^{20}_D 1.3932). The latter was identified by the infrared spectrum. The products isolated and the amounts of them are given in Table 1.

Methyl butyrate. The organic layer (167 g) was distilled. After distillation of the monomer there remained 27 g of viscous liquid. The reaction product was vacuum distilled. The distillation curve is shown in Fig. 3. Fractions 3 and 4* (b.p. 114-117° at 8 mm, n^{20}_D 1.4341, d_4^{20} 1.0262) consisted of the dimer of methyl butyrate.

Found %: C 59.40; H 8.87. M 212; MR_D 51.33. $C_{10}H_{18}O_4$. Calculated %: C 59.38; H 8.97. M 202; MR_D 51.69

Dimethyl suberate has n^{20}_D 1.43408, d_4^{20} 1.0217 [7]. A 10 ml sample of the dimer methyl butyrate was hydrolyzed by boiling with dilute sulfuric acid. The solution was evaporated to a residual volume of about 50 ml. The precipitated crystals of the dicarboxylic acid (0.5 g, m.p. 130°) were recrystallized twice from water, when they had m.p. 140° (suberic acid has m.p. 140° [8]).

Found %: C 55.01; H 8.30. Equiv. 88.0. $C_8H_{14}O_4$. Calculated %: C 55.16; H 8.10. Equiv. 87.1.

Thus, the dimer of methyl butyrate contained dimethyl suberate. Fraction 7 consisted of the trimer of methyl butyrate contaminated with acid products. It had b.p. 135-145° at 1 mm, n^{20}_D 1.4539, d_{20}^{20} 1.0934.

Found %: C 59.85; H 8.30. M 319. $C_{15}H_{26}O_6$. Calculated %: C 59.59; H 8.67. M 302.

Fraction 8 was the tetramer of methyl butyrate with b.p. 175-200° at 1 mm, n^{20}_D 1.4625, d_{20}^{20} 1.1159.

Found %: C 59.90; H 8.60. M 380. $C_{20}H_{34}O_8$. Calculated %: C 59.68; H 8.51. M 402.

* The first fractions contained some butyric acid.

Ethyl propionate. The organic layer (140 g) was distilled. Distillation of the ethyl propionate yielded 18 g of residue (n^{20}_D 1.4345). Fractionation of the latter gave the following fractions: fraction 1, b.p. 125-130° at 10 mm, n^{20}_D 1.4270, d_{20}^{20} 1.014; fraction 2, b.p. 150-160° at 14 mm, n^{20}_D 1.4398, d_{20}^{20} 1.079, and a viscous, tarry residue. Fraction 1 corresponded in constants to diethyl adipate (b.p. 127° at 13 mm, n^{20}_D 1.4272, d_4^{20} 1.0076 [8]) and fraction 2 to monoethyl adipate (b.p. 163° at 10 mm, n^{20}_D 1.4388, d^{20} 1.081 [8]). Both fractions were hydrolyzed by boiling with dilute sulfuric acid. In both cases we isolated crystals of adipic acid (m.p. 149-151°). The latter were identified by the infrared spectrum in the region of 2-14 μ.

The viscous tarry residue evidently consisted of oligomers of ethyl propionate and monoethyl adipate. The latter were not isolated. From the aqueous layer we isolated acetaldehyde as the 2,4-dinitrophenylhydrazone with m.p. 141° (from alcohol). Literature data: m.p. 147° and 168° [9].

Found %: C 42.97; H 3.52. $C_8H_8O_4N_4$. Calculated %: C 42.86; H 3.59.

Extraction of the aqueous layer with diethyl ether yielded propionic acid, which was identified by the infrared spectrum.

Dimethyl adipate. The organic layer (310 g) was distilled. After distillation of the starting dimethyl adipate we obtained 49 g of a viscous residue (n^{20}_D 1.4535). The product was vacuum distilled. We isolated two main fractions: fraction 1 with b.p. 148-158° at 8 mm, n^{20}_D 1.4415 (18.5 g); fraction 2 with b.p. 200-235° at 5 mm, n^{20}_D 1.4595 (20 g), and 10.5 g of a very viscous, acid, tarry residue. Fraction 1 was redistilled. We isolated monomethyl adipate (b.p. 155° at 6 mm, n^{20}_D 1.4410, d_{20}^{20} 1.128). Hydrolysis of the monomethyl adipate obtained gave adipic acid (65% yield), which was identified by the infrared spectrum. Fraction 2 was dissolved in ether and neutralized with aqueous bicarbonate. Distillation yielded a dimer of dimethyl adipate, which was a colorless, viscous liquid with b.p. 210-215° at 3 mm, n^{20}_D 1.4616, d_{20}^{20} 1.1584.

Found %: C 55.30; H 7.53. M 360; MR_D 80.92. $C_{16}H_{26}O_8$. Calculated %: C 55.48; H 7.57. M 346; MR_D 80.70.

The tarry residue was evidently oligomers of di- and monomethyl adipate.

Butyl acetate. Fractionation of the product from the reaction of butyl acetate with hydroxyl radicals (11 g) yielded approximately equal amounts of an individual dimer and oligomers of butyl acetate (as a residue). The dimer of butyl acetate was a colorless liquid with b.p. 123-125° at 4 mm, n^{20}_D 1.4405, d_{20}^{20} 0.9967.

Found %: C 63.02; H 9.85. Equiv. 117.5; M 242; MR_D 60.95. $C_{12}H_{22}O_4$. Calculated %: C 62.59; H 9.63. Equiv. 115.1; M 230; MR_D 60.92.

The oligomers formed a light brown, very viscous liquid with n^{20}_D 1.4732, d_{20}^{20} 1.079. M 610.

A mixture of 72 g of the dimer of butyl acetate, 30 g of NaOH, 40 ml of water, and 250 ml of ethylene glycol was boiled under reflux for 3 hr. The ethylene glycol was removed in vacuum. The residue in the flask was dissolved in water and diethyl ether. The layers were separated and the aqueous layer extracted repeatedly with ether. We obtained 25 g of a glycol, which consisted of a very viscous liquid with b.p. 142-144° at 9 mm, n^{20}_D 1.4607, d_{20}^{20} 0.9612.

Found %: C 65.33; H 12.26. MR_D 42.26. $C_8H_{18}O_2$. Calculated %: C 65.70; H 12.40. MR_D 42.19.

The glycol isolated was not oxidized by periodic acid. A 32 g sample of the glycol was dehydrated over alumina at 270°. We obtained 22 g (83% yield) of a mobile greenish liquid with b.p. 140-145°, n^{20}_D 1.4425, d_{20}^{20} 0.8543.

As has already been mentioned, the infrared spectrum of the substance obtained did not contain absorption bands characteristic of a hydroxyl group or a double bond, but an absorption band characteristic of a tetrahydrofuran ring (Fig. 1).

Found %: C 74.40; H 12.05. M 135; MR_D 39.65. $C_8H_{16}O$. Calculated %: C 74.93; H 12.57. M 128; MR_D 38.58.

The authors would like to thank Ts. N. Roginskaya for the spectral analyses.

SUMMARY

1. In the reaction of aliphatic esters with hydroxyl radicals there is simultaneously dehydrodimerization and oxidation of the esters.

2. From the dehydrodimerization products of methyl isobutyrate, methyl butyrate, ethyl propionate, and butyl acetate, we isolated the following compounds: the dimethyl esters of α,α'-dimethyladipic, α,α,α'-trimethylglutaric, and tetramethylsuccinic acids; dimethyl suberate; diethyl adipate and 2,3-diethylbutane-1,4-diol diacetate, respectively.

3. The dimers obtained reacted, in their turn, with hydroxyl radicals to form trimers and tetramers.

4. The reaction mechanism is discussed.

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INVESTIGATIONS IN THE ANTHRAQUINONE SERIES

XXXIII. REACTION OF ANTHRAQUINONESULFONIC ACIDS WITH BASIC DYES*

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In a search for specific reactions for various anthraquinonesulfonic acids [1], we studied the possibility of their reaction with some basic dyes. The production of color lakes from basic dyes consists of converting the latter into water-insoluble compounds with various precipitants. The latter include various acidic dyes [2]. There are reports on the preparation of finely disperse lakes from basic dyes by precipitation with various arenesulfonic acids [3]. Among the latter, 1-nitroanthraquinone-5-sulfonic acid is recommended. Some patents cover the use of wetting and dispersing agents like alkylated aromatic carboxylic and sulfonic acids for the precipitation of finely disperse lakes from basic dyes [4].

Our experiments show that in the direct interaction of solutions of isomeric anthraquinonemono- and disulfonic acids or their soluble salts with solutions of basic dyes there is a sharp deepening of the initial color of the dye solution. For example, when a 1% solution of Malachite green (C. I. 657) [5], which has a greenish blue color, is added to excess of a solution of isomeric anthraquinonesulfonic acids, there are successive changes in color in the following order: greenish blue → blue → bluish green → dark green. The reaction of anthraquinone-2,6-disulfonic acid with a 1% solution of rhodamine C (C. I. 749) leads to a change in the color of the initial dye solution from red to intense blue-red. This phenomenon is characteristic of relatively concentrated solutions with a considerable excess of the anthraquinonesulfonic acid. In a number of cases, the reaction leads to the formation of amorphous or often completely crystalline colored precipitates. The precipitated compounds normally dissolve in the mother solution on heating, in excess anthraquinonesulfonic acid, or on addition of alcohol. The formation of difficultly soluble compounds from auramine (C. I. 655) and various anthraquinonesulfonic acids is most characteristic. The action of anthraquinone-1,5-disulfonic acid on a solution of this dye is particularly interesting and leads to the instantaneous formation of a bright orange-red crystalline precipitate. On drying, the substance becomes bright orange with the loss of water of crystallization, but gradually returns to the original color on standing in air. The precipitation is exceptionally clear and auramine may be regarded as a reagent for anthraquinone-1,5-disulfonic acid. The sensitivity of the reaction (visible precipitation) is 1 part of free anthraquinone-1,5-disulfonic acid in 10,000 parts of water. The reactions of a solution of auramine with anthraquinone-2,6-disulfonic acid and anthraquinone-β-sulfonic acid are quite specific. The former gives a dark yellow crystalline precipitate, which is difficultly soluble in water, but soluble in dilute alcohol. The sensitivity of the reaction is 1 part of anthraquinone-2,6-disulfonic acid in 20,000 parts of water. The latter acid forms a bright yellow-orange crystalline precipitate with a reaction sensitivity of 1 part of the sodium salt of anthraquinone-β-sulfonic acid in 75,000 parts of water. The remaining isomeric anthraquinonesulfonic acids also form characteristic colored precipitates with auramine, but with lower reaction sensitivities. Chrysoidin (C. I. 20) also gave interesting results with anthraquinonesulfonic acids. The specific reaction of the latter with anthraquinonemonosulfonic acids, in contrast to anthraquinonedisulfonic acids, formed precipitates which were difficultly soluble in water. The sensitivity of the precipitation for potassium anthraquinone-α-sulfonate was 1 part in 5000 parts of water. The formation of crystalline precipitates by anthraquinonesulfonic acids and basic dyes occurs both in neutral and weak sulfuric acid solutions, but not in hydrochloric acid solutions. A few drops of hydrochloric acid dissolve the precipitate formed by the reaction of anthraquinonesulfonic acid and dye solutions. None of the colored crystalline precipitates of compounds from anthraquinonesulfonic acids and basic dyes, which are usually hydrochlorides of colored bases, contain chlorine. This and the results of analyses of the substances for water or

* For communication XXXII, see ZhOKh, 31, 1917 (1961).

Color of Compounds of Auramine with Some Anthraquinonesulfonic Acids as Fine Powders

Compound	Color	λ mμ
Auramine*	Lemon yellow	440
Auramine and anthraquinone- α-sulfonic acid	Orange	460
Auramine and anthraquinone- β-sulfonic acid	Yellow-orange	480
Auramine and anthraquinone-1,5-disulfonic acid	Bright orange-red	490
Auramine and anthraquinone-2,6-disulfonic acid	Dark yellow	452

* The absorption curve of auramine in the solid state is a steeply falling curve without any clearly expressed maximum (see figure); in the table we therefore give the value of λ for the absorption limit.

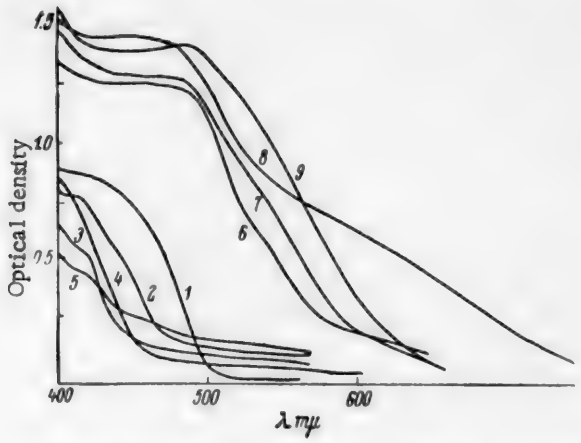
crystallization and nitrogen indicate that the formation of the new compounds is a double exchange reaction. There is simple salt formation between the weak dye base and the strong anthraquinonesulfonic acid.

$$[R—N(X)_2] \cdot HCl + HSO_3R' \longrightarrow [R—N(X)_2] \cdot HSO_3R' + HCl$$
$$X = H, \text{ Alk.}$$

Some salts of dye bases and anthraquinonesulfonic acids have sharp melting points and crystallize in well-formed crystals and are similar in this respect to many salts of aromatic sulfonic acids with various amines. The salt of auramine with anthraquinone-1,5-disulfonic acid in the solid form is bright orange-red, but dissolves in water on heating to form a more yellow solution. On cooling, the solution again deposits the orange-red substance. The addition of acetic acid to a yellow aqueous solution of this compound does not change the color, while the addition of sulfuric and particularly hydrochloric acid produces the heightening of color usual with basic dyes as a result of the formation of a diacidic salt. As was noted above, under conditions where the reaction of solutions of a basic dye and an anthraquinonesulfonic acid leads only to an appreciable change in the shade and intensity of the color of the dye solution, this state corresponds to the equilibrium between the dye hydrochloride and the soluble saltlike compound of the anthraquinonesulfonic acid and the dye base.

To assess the relative depths of color of the compounds in the solid state, we plotted the reflection spectra of fine powders rubbed into paper. The reverse side of normal photographic paper (backing) was found to be most suitable for this purpose. The reflection spectra were measured on an SF-2M recording spectrophotometer. The spectrum was recorded in optical density units [6]. This recording method is convenient in that it facilitates the examination of effects and makes it possible to compare the absorption spectra of powder surfaces with those of the substances in solution. An examination of the absorption curves (see figure) shows that the spectrum of a substance obtained by the reaction of a basic dye (for example, auramine) and isomeric anthraquinonemono- and disulfonic acids differs from the spectra of the starting compounds. There is a strong bathochromic displacement of the absorption band for the same dye. The magnitude of the displacement depends to some extent on the structure of the isomeric anthraquinonesulfonic acid (see table). The absorption spectra of the powders show that the reaction of solutions of a basic dye (for example, auramine) and anthraquinonesulfonic acids forms new compounds. While the colors of the compounds obtained from auramine and isomeric anthraquinonesulfonic acids as powders differed from that of auramine itself, the colors of their water or alcohol solutions at concentrations of 10^{-4}–10^{-5} mole/liter did not differ at all from the color of the starting dye. The absorption curves of auramine compounds in such solutions were practically the same with a single clearly expressed maximum, which had a hypsochromic shift of 1-2 mμ. The curves had a higher molar absorption coefficient (optical density) than the starting dye as a result of the superposition of the absorption bands of the starting dye base and the anthraquinonesulfonic acid. Elimination of the color of compounds of auramine or other basic dyes with anthraquinonesulfonic acids was observed in aqueous solutions and in such solvents as methanol, ethanol, acetone, chloroform, carbon tetrachloride, benzene, n-octane, and nitrobenzene and even on grinding with vaseline oil. When more concentrated solutions ($10^{-2} - 4 \cdot 10^{-2}$ mole/liter) of compounds of a dye with anthraquinonesulfonic acids were prepared in the cold, their colors differed appreciably from both those of

less concentrated solutions of these compounds and those of solutions of the starting dyes. There was also an appreciable and, most often, bathochromic change in the color of concentrated solutions of compounds of a dye base with an anthraquinonesulfonic acid with excess of the latter. However, it was not possible to plot the absorption spectra of such concentrated solutions. Under these conditions, the absorption of a free anthraquinonesulfonic acid is very great and this made it impossible to detect the absorption of either the starting dye or its compounds with the sulfonic acid. The latter compounds in the solid state correspond to an undissociated salt-like form of the dye base and the anthraquinonesulfonic acid and on solution, they readily dissociate into their constituent ions. At the same time, in view of all the above facts, it cannot be considered that the reason for the color of these compounds



Absorption spectra of the surface of powdered derivatives of auramine and anthraquinonesulfonic acids. 1) Auramine; 2) anthraquinone-α-sulfonic acid; 3) anthraquinone-β-sulfonic acid; 4) anthraquinone-1,5-disulfonic acid; 5) anthraquinone-2,6-disulfonic acid; 6) auramine with anthraquinone-α-sulfonic acid; 7) auramine with anthraquinone-β-sulfonic acid; 8) auramine with anthraquinone-2,6-disulfonic acid; 9) auramine with anthraquinone-1,5-disulfonic acid.

is solely the undissociated state of the substance in the solid phase, which is composed of the dye base and the new chromophore, namely, the anthraquinonesulfonic acid. It can be assumed that under certain conditions there also arise exomolecular forces between the electron-donor part of the molecule (the dye cation) and the electrophilic part of another molecule (the anthraquinonesulfonic acid anion). The properties of the given compounds differ appreciably from those of salts of anthraquinonesulfonic acids and aromatic amines. An overwhelming majority of the latter are either colorless or pale yellow. According to our observations, only N-substituted amines do not form salts with isomeric anthraquinonesulfonic acids, i.e., the latter behave like benzenesulfonic acid [7]. We also established that while benzenesulfonic acid does not react with a solution of auramine, isomeric nitrobenzenesulfonic acids form crystalline precipitates with this dye. These compounds behave like anthraquinonesulfonic acids. The absorption spectra of the surface of powders of these compounds of auramine with mononitrobenzenesulfonic acids show a considerable bathochromic shift in comparison with the spectrum of pure auramine. The maximum shift was observed with the compound with o-nitrobenzenesulfonic acid.

We established that in many cases, the addition of anthraquinonesulfonic acids to the dye bath in the dying of animal fibers, nitro film, and acetate silk with basic dyes improves the dye-receptivity and increases the brightness of the color.

EXPERIMENTAL

Preparation of salts of anthraquinonesulfonic acids and basic dyes. To a 1-5% solution of the anthraquinonesulfonic acid or its sodium or potassium salt in water or in 0.5-3.0% sulfuric acid was added excess of a 1% solution of the basic dye at 20-40°. The mixture was cooled and the precipitate collected, washed with a little iced water, pressed out, and dried in air.

1) A 0.84 g sample of anthraquinone-1,5-disulfonic acid (m.p. 312°) in 20 ml of water and auramine formed needles with m.p. 206° in 95.9% yield. The substance was very difficultly soluble in cold water, more soluble in methanol and ethanol, and insoluble in dioxane and hydrocarbons in the cold.

Found %: H_2O 11.75. $C_{14}O_2H_6(SO_3H)_2 \cdot (C_{17}N_3H_{22})_2 \cdot 7H_2O$. Calculated %: H_2O 11.85. Found %: N 9.19. $C_{14}O_2H_6(SO_3H)_2 \cdot (C_{17}N_3H_{22})_2$. Calculated %: N 9.29.

2) Compound of auramine with anthraquinone-α-sulfonic acid.

Found %: H_2O 11.20. $C_{14}O_2H_7SO_3H \cdot C_{17}N_3H_{22} \cdot 4H_2O$. Calculated %: H_2O 11.46. Found %: N 7.71. $C_{14}O_2H_7SO_3H \cdot C_{17}N_3H_{22}$. Calculated %: N 7.56.

3) A solution of 0.12 g of the sodium salt of anthraquinone-β-sulfonic acid in 6 ml of 3% sulfuric acid and auramine formed a substance in quantitative yield. The product crystallized from dilute alcohol as fine yellow-orange crystals.

Found %: H_2O 3.13. $C_{14}O_2H_7SO_3H \cdot C_{17}N_3H_{22} \cdot H_2O$. Calculated %: H_2O 3.45. Found %: N 7.61. $C_{14}O_2H_7SO_3H \cdot \cdot C_{17}N_3H_{22}$. Calculated %: N 7.56.

4) The substance obtained by the reaction of anthraquinone-2,6-disulfonic acid with auramine did not contain water of crystallization and had m.p. 238°.

Found %: N 9.33. $C_{14}O_2H_6(SO_3H)_2 \cdot (C_{17}N_3H_{22})_2$. Calculated %: N 9.29.

5) Auramine reacted with anthraquinone-1,7- and 2,7-disulfonic acids to form fine precipitates, which dissolved in excess sulfonic acid or on heating. The salt with the 2,7-disulfonic acid was light orange.

Found %: H_2O 3.71. $C_{14}O_2H_6(SO_3H)_2 \cdot (C_{17}N_3H_{22})_2 \cdot 2H_2O$. Calculated %: H_2O 3.82. Found %: N 9.27. $C_{14}O_2H_6(SO_3H)_2 \cdot (C_{17}N_3H_{22})_2$. Calculated %: N 9.29.

6) Anthraquinone-1,8-disulfonic acid and auramine in aqueous solution formed a golden orange precipitate. The substance was difficultly soluble in water, but soluble in alcohol. It did not contain water of crystallization and did not melt when heated to 370°.

Found %: N 9.27. $C_{14}O_2H_6(SO_3H)_2 \cdot (C_{17}H_3N_{22})_2$. Calculated %: N 9.29.

7) A solution of 0.2 g of potassium anthraquinone-α-sulfonate in 50 ml of water, made weakly acid with sulfuric acid, reacted with chrysoidin to give a 99.5% yield of a precipitate of fine orange-red needles, which were insoluble in hot water and difficultly soluble in alcohol.

Found %: H_2O 3.78. $C_{12}N_4H_{12}HSO_3 \cdot C_{14}O_2H_7 \cdot H_2O$. Calculated %: H_2O 3.47. Found %: N 11.3. $C_{14}O_2H_7SO_3H \cdot C_{12}N_4H_{12}$. Calculated %: N 11.2.

8) With chrysoidin, anthraquinone-1,5-disulfonic acid formed a brick-red precipitate, which was soluble in hot water and crystallized from it as clusters of fine needles.

Found %: H_2O 2.3. $[C_{12}N_4H_{12}]_2 \cdot C_{14}O_2H_6[SO_3H]_2 \cdot H_2O$. Calculated %: H_2O 2.22. Found %: N 14.37. $C_{14}O_2H_6(SO_3H)_2 \cdot (C_{12}N_4H_{12})_2$. Calculated %: N 14.14.

9) Isolation of anthraquinonemonosulfonic acids from solutions of mixtures of them with anthraquinonedisulfonic acids. A mixture of 0.1 g of anthraquinone-α-sulfonic acid and 0.1 g of anthraquinone-β-sulfonic acid in 20 ml of 3.5% sulfuric acid was precipitated with excess of a 1% solution of chrysoidin. The yield of the mixture of chrysoidin salts of anthraquinonemonosulfonic acids was 99.45%. To a mixture of 0.1 g of anthraquinone- α-sulfonic acid, 0.05 g of anthraquinone-β-sulfonic acid, 0.0254 g of anthraquinone-1,5-disulfonic acid, and 0.0252 g of anthraquinone-2,6-disulfonic acid in 20 ml of 3.5% sulfuric acid was added excess of a 1% solution of chrysoidin at 80°. After the mixture had been stirred for 15 min, the precipitate was collected, washed with a small amount of hot water, and dried in a vacuum drying cupboard at 100°. The yield of the mixture of chrysoidin salts of anthraquinone monosulfonic acids was 95.15%.

10) The addition of anthraquinone-2,6-disulfonic acid to a 1% aqueous solution of rhodamine C (C. I. 749) strongly increased the intensity of the color of the solution, eliminated the characteristic fluorescence, and produced a dark red amorphous precipitate.

Found %: H_2O 4.04. $C_{14}O_2H_6(SO_3H)_2 \cdot [(C_2H_5)_2NC_6H_3OC \cdot C_6H_4COOH \cdot C_6H_3N(C_2H_5)_2] \cdot 3H_2O$. Calculated %: H_2O 4.12. Found %: N 4.56. $C_{14}O_2H_6(SO_3H)_2 \cdot C_{56}N_4O_6H_{62}$. Calculated %: N 4.46.

11) Methylene Blue (C. I. 922) and anthraquinone-2,6-disulfonic acid formed a fine crystalline precipitate, which dissolved readily in excess of the disulfonic acid with the development of an intense blue-green color.

Found %: H_2O 7.41. $[(CH_3)_2NC_6H_3NSC_6H_3N(CH_3)_2]_2 \cdot C_{14}O_2H_6(SO_3H)_2 \cdot 4H_2O$. Calculated %: H_2O 7.38. Found %: N 8.79. $C_{32}N_6S_2H_{48} \cdot C_{14}O_2H_6(SO_3H)_2$. Calculated %: N 8.86.

Anthraquinone-1,7-disulfonic acid produced a change in the color of a 1% aqueous solution of Methylene Blue from blue to green. The remaining isomeric anthraquinonesulfonic acids did not produce appreciable changes in the color of the dye solution.

12) Basic Bright Green (C. I. 662) and anthraquinone-β-sulfonic acid formed a flocculent blue precipitate, which dissolved readily when alcohol was added. Anthraquinone-1,7-disulfonic acid and the dye solution gave a finely crystalline green precipitate, which was difficultly soluble in water; the mother solution was dark green. Anthraquinone-2,7-disulfonic acid and the dye solution gave a precipitate of fine blue needles, which were difficultly soluble in water. The other isomeric anthraquinonesulfonic acids behaved like hydrochloric acid or a concentrated solution of sodium chloride, i.e., heightened the color of the dye solution to an olive-yellow as a result of the formation of a diacidic salt.

13) Rosaniline hydrochloride and an aqueous solution of anthraquinone-2,6- or 1,5-disulfonic acid gave an amorphous precipitate, which was soluble in water on heating; an intensely colored amorphous precipitate was formed with anthraquinone-1,8-disulfonic acid.

SUMMARY

1. Specific reagents were found for various anthraquinonesulfonic acids and these were basic dyes, for example, auramine, chrysoidin, etc.

2. The absorption spectra of these compounds showed a strong bathochromic shift in comparison with the starting dye, which was not only the result of the undissociated state of the substance in the solid phase, but also the possible manifestation of exomolecular forces.

3. Analogous color phenomena were found in the precipitates obtained by the reaction of isomeric nitrobenzenemonosulfonic acids with auramine.

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CHEMICAL INVESTIGATION OF SCHIZANDRA CHINENSIS

I. SCHIZANDRIN AND RELATED COMPOUNDS

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Schizandra chinensis Bail. (fam. Magnoliaceae) is a small liana, which occurs widely in the forests of the Far East. The leaves, fruit, and seeds of Schizandra chinensis have long been used in the folk medicine of countries of the East, including Chinese medicine, as a stimulant. A whole series of studies have been devoted to the evaluation of various preparations of Schizandra chinensis (see, for example, [1]); the action of extracts of Schizandra chinensis seeds on the central nervous system has been studied in detail [2] and there are reports of the use of Schizandra chinensis in psychiatry [3] and for the treatment of cardiac [4] and some other diseases [5, 6].

Although the isolation and the determination of the structure of the active principles of Schizandra chinensis are of undoubted interest, there are hardly any data on this problem. The only data were reported by D. A. Balandin [7], who isolated from the oil of Schizandra chinensis seeds an individual substance, which he called schizandrin; according to the data of this author, schizandrin has m.p. 129.7° and the composition $C_{23}H_{32}O_6$. On the basis of a study of the pharmacological activity, the hypothesis was put forward [8] that schizandrin is one of the active principles of Schizandra chinensis and is responsible for its stimulating action. The study of schizandrin could have served as the starting point for an investigation of Schizandra chinensis, but the data of D. A. Balandin [7] were quite inadequate and needed reexamination and likewise the structural formula of schizandrin he proposed without sufficient basis.

We first attempted to isolate schizandrin using the data of D. A. Balandin. The method he described, which consisted of extraction of the seeds with ligroin, repeated extraction of the oil thus obtained with 85% alcohol, subsequent precipitation of the inert materials with lead acetate, and crystallization of the schizandrin by slow evaporation of its aqueous alcohol solution, gave us a crystalline substance, which was identical with D. A. Balandin's schizandrin* in melting point and specific rotation. The substance did not depress the melting point of the schizandrin sample mentioned.

On the basis of elementary analysis data and determination of the molecular weight of the substance, we determined the empirical formula of schizandrin more accurately; according to our data, it has m.p. 130°, $[\alpha]_D$ + 91.5° and the composition $C_{23}H_{32}O_7$.

We then made a more detailed investigation of the oil of Schizandra chinensis seeds. After schizandrin had been shown to be stable to alkalis by special experiments, we hydrolyzed the Schizandra chinensis oil and isolated the unhydrolyzed part.

By paper chromatography in two systems (see experimental section), it was possible to show that in addition to schizandrin, the unhydrolyzed fraction contained six other substances which absorbed in the ultraviolet like schizandrin itself. We called these substances α-, β-, γ-, δ-, and ε-schizandrins and schizandrol, respectively, in order of increasing polarity and according to chromatographic data (see Figs. 1 and 2).

Schizandrin, β-, γ-, δ-, and ε-schizandrins, and schizandrol gave a positive Näule reaction [9], which is characteristic of substances containing a pyrogallol grouping, and the ultraviolet spectra of the γ-schizandrin, schizandrol, and schizandrin, which were isolated in a discrete state, were very similar, indicating that their chemical structures had common features.

* The authors of the present article are very grateful to N. N. Vorozhtsov Jr., for providing the sample of schizandrin isolated by the late D. A. Balandin.

To separate the substances present in the unhydrolyzed part of the Schizandra chinensis oil, we then used adsorption chromatography on alumina (see experimental). As a result of this, together with a mixture of terpenes with b.p. 96-100° at 2 mm, which we did not investigate in detail, we isolated schizandrin, schizandrol, and γ-schizandrin in a discrete state.

The other components of the oil have not been separated as yet as a result of the low content of them. The schizandrin content of the unhydrolyzed fraction was 16% (0.64%, calculated on the seeds), the schizandrol content 3.2% (0.13% in the seeds), and γ-schizandrin 2.5% (0.10% in the seeds). The schizandrin isolated in accordance with this scheme was found to be completely identical to the sample isolated by D. A. Balandin's method and as the method we developed is much simpler and makes it possible to extract the schizandrin more fully, we subsequently used only this method.

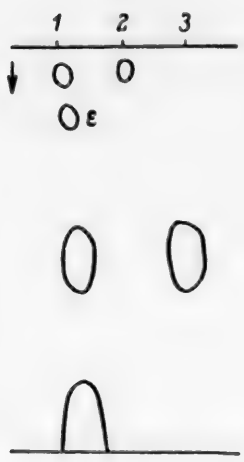

Fig. 1. Composition of unhydrolyzed fraction according to data from paper chromatography in system I. 1) Unhydrolyzed fraction; 2) schizandrol; 3) schizandrin.

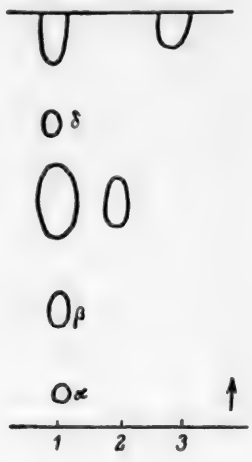

Fig. 2. Composition of unhydrolyzed fraction according to data from paper chromatography in system II. 1) Unhydrolyzed fraction; 2) γ-schizandrin; 3) schizandrin.

Analysis of schizandrin for functional groups showed that it contained five OCH_3 groups and one OH group.

The infrared spectrum of schizandrin (Fig. 3) confirmed the presence of a hydroxyl group and indicated the absence of carbonyl, carboxyl, and lactone groups. The intense absorption band at 1600 cm^{-1} indicates the presence of an aromatic system in the schizandrin molecule.

Schizandrin did not react with acetic anhydride or p-nitrobenzoyl chloride in pyridine, was not methylated by dimethyl sulfate and alkali, and did not give the normal qualitative reactions for phenolic compounds. Thus, the hydroxyl in schizandrin is not phenolic and is most likely attached to a tertiary carbon atom. Schizandrin was not hydrogenated over $Pd/BaSO_4$ in alcohol or Pt in acetic acid at room temperature and atmospheric pressure. In connection with this it must be assumed that the data on the presence in schizandrin of two double bonds [7], which were found by bromination of schizandrin, are incorrect as no allowance was made for the ready bromination of the highly active aromatic nuclei of schizandrin, which we established in special experiments.

Thus, the formula of schizandrin may be represented in the form $C_{18}H_{16}(OCH_3)_5(OH)(O)$.*

Analysis data for schizandrol indicate the formula $C_{21}H_{28}O_7$ and on the basis of analysis for methoxyl groups, this may be developed into

$$C_{18}H_{16}(OH)_3(OCH_3)_3(O)$$

allowing for the fact that the infrared spectrum does not contain frequencies of carbonyl, carboxyl, and lactone groups. Schizandrol gave a green color with $FeCl_3$, coupled with diazobenzenesulfonic acid, and, consequently, is a phenol. A comparison of the expanded formulas of schizandrin and schizandrol shows that schizandrol has two hydroxyl groups more and two methoxyl groups less than schizandrin. In view of the phenolic nature of schizandrol and the similarity of its infrared and ultraviolet spectra to those of schizandrin, it is natural to assume that schizandrin is a methylated derivative of schizandrol.

* According to new data we have obtained, schizandrin has the formula $C_{18}H_{13}(OCH_3)_5(OH)$[added during proofreading].

In actual fact, methylation of schizandrol with dimethyl sulfate in an alkaline medium gave a substance which was completely identical to schizandrin in ultraviolet and infrared spectra and specific rotation and a mixed melting

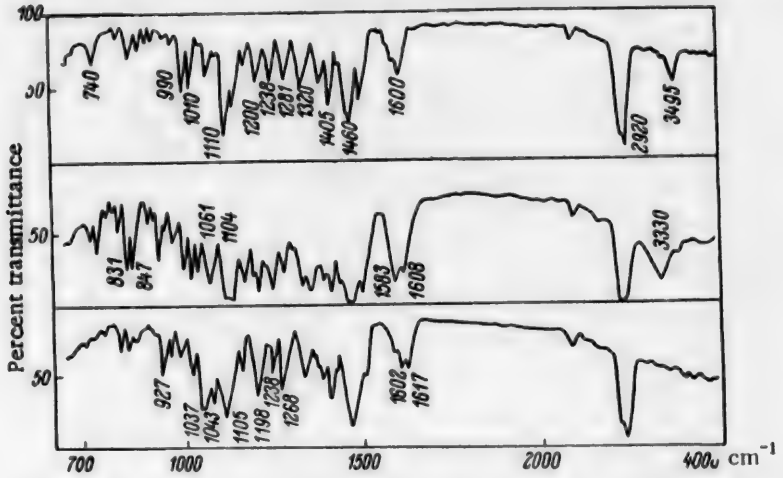

Fig. 3. Infrared spectra of schizandrin, schizandrol, and γ-schizandrin. 1) Schizandrin; 2) schizandrol; 3) γ-schizandrin.

point was not depressed. Schizandrol did not couple with mono-N-chloroquinonimine [10] and did not give a color with ammonium molybdate [11], which indicates the presence of para-substituents in the aromatic nuclei relative to the phenolic hydroxyls and also the absence of an o-dihydroxybenzene grouping. Acetylation of schizandrol with acetic anhydride in pyridine gave schizandrol diacetate with the composition $C_{25}H_{32}O_9$. The infrared spectrum of schizandrol diacetate retained the OH-group frequency at 3520 cm^{-1} and there appeared a carbonyl frequency of an acetoxyl grouping at 1745 cm^{-1}. This confirms that together with two phenolic hydroxyls, schizandrol contains a hydroxyl group analogous to the hydroxyl group of schizandrin.

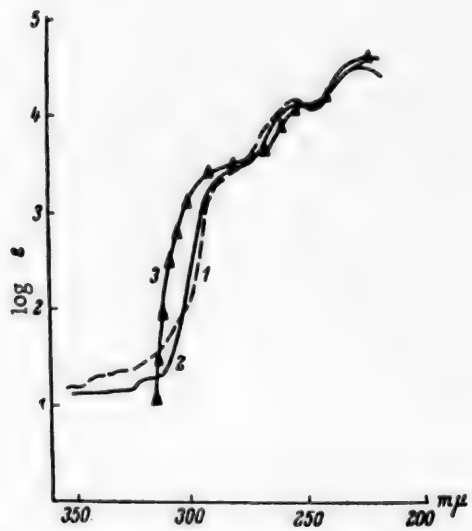

Fig. 4. Ultraviolet spectra of schizandrin, schizandrol, and γ-schizandrin. 1) Schizandrin; 2) schizandrol; 3) γ-schizandrin.

γ-Schizandrin has the empirical formula $C_{23-24}H_{28-30}O_6$ and contains three methoxyl groups. According to the infrared spectrum, in contrast to schizandrol and schizandrin, it does not contain OH groups and it also does not contain carbonyl, carboxyl, or lactone groups.

The elucidation of the structure of the substances isolated and the isolation of further components from Schizandra chinensis oil are continuing at the present time and will be the subject of future communications.

The elementary and functional group analyses were carried out under the direction of M. N. Chumachenko; the infrared and ultraviolet spectra were plotted by L. B. Senyavina, to whom the authors are very grateful.

EXPERIMENTAL

The infrared spectra were plotted with a Hilger spectrophotometer (model H-800) with NaCl prisms; the samples were made up in vaseline oil. The ultraviolet spectra were plotted on an SF-4 spectrophotometer with alcohol solutions. Alumina of activity II was used for adsorption chromatography. The fractions were analyzed by chromatography on paper (type "M" of the Volodarskii Leningrad factory) impregnated with a 20% solution of ethylene glycol in methanol or a 10% solution of vaseline oil in benzene. In the first case the mobile phase was a m-xylene–n-octane (1 : 9) mixture, saturated with ethylene glycol (system I), and in the second case, 70% aqueous methanol

TABLE 1. Chromatographic Separation of Unhydrolyzed Fraction of Schizandra chinensis Oil on Alumina

Fraction No.	Solvent	Volumes (liters)	Residue (g)	Composition according to paper chromatography data[a]
1	Isooctane	1	5	b
2	Isooctane – benzene (1 : 1)	1	1	c
3	Benzene	2	3.5	α-, β-, γ-, δ-Schizandrins[d]
4	Benzene	2	15	α-,[e] β-, γ-,[f] δ-Schizandrins[d]
5	Benzene – chloroform (1 : 1)	1	2	γ-, δ-Schizandrins, schizandrin
6	Chloroform	2	18	Schizandrin[g]
7	Chloroform	2	14	Schizandrin, ε-schizandrin, schizandrol[h]
8	Chloroform – methanol (1 : 1)	1	5	Schizandrin, ε-schizandrin, schizandrol[h]
9	Methanol	1	6.5	Schizandrol[i]

Footnote: [a]As the spots were detected by the ultraviolet absorption and the Mäule reaction, substances which could not be detected in this way do not appear in this column. However, their presence considerably hampered the isolation and purification of schizandrin and its analogs. [b]Fraction 1 was a clear liquid with a characteristic terpene odor, b.p. 96-100° at 2 mm, n^{20}_D 1.4990, d_4^{20} 0.9241, $[\alpha]_D$ – 7.6; it gave a positive reaction with tetranitromethane. [c]Fraction 2 was not investigated in detail; it was a viscous oil, which did not contain substances that absorb in the ultraviolet. [d]In system II, the R_f values of α-, β-, γ-, and δ-schizandrins equals 0.06, 0.18, 0.50, and 0.66, respectively. In addition, there were two spots which fluoresced in the ultraviolet and had R_f 0.05 and 0.44. [e]α-Schizandrin did not give a Mäule reaction and was detected by the ultraviolet absorption. [f]The spot of γ-schizandrin was most intense. [g]Schizandrin has R_f 0.68 in system I. [h]Schizandrol and ε-schizandrin have R_f 0.09 and 0.24, respectively, in system I. [i]The fraction contained a large amount of tarry substances.

(system II). System I was used for descending chromatography and system II for ascending chromatography at 19-22°. The spots of schizandrin and its analogs were detected by their absorption in the ultraviolet or by Maule's reaction [9]. The melting points are not corrected. The ligroin used in the work had b.p. 60-80°.

I. Extraction of oil from seeds. A 1.8 kg sample of ground seeds of Schizandra chinensis (prepared by the Khabarovsk Main Administration of Pharmacies in 1936-1957) was extracted for 2 days with 5 liters of ligroin in a Soxhlet apparatus. Removal of the ligroin gave 500 g (28% of the weight of the seeds) of an oil, which was extracted with methanol (20 times with 200 ml portions). Removal of the methanol yielded a methanol-soluble fraction (300 g, 60% of the weight of the oil), which was treated in the same way with 85% aqueous methanol. This yielded 200 g of a fraction that was soluble in aqueous methanol. The fractions that were not soluble in aqueous methanol did not contain schizandrin and contained only a very small amount of λ- and β-schizandrins, according to data from paper chromatography in systems I and II.

II. Hydrolysis of oil and isolation of unhydrolyzed fraction. A 200 g sample of the oil fraction which was soluble in 85% methanol was heated with 1 liter of 1 N sodium hydroxide in 85% methanol for 6 hr. The solution was evaporated in vacuum with the periodic addition of water so that the volume of the mixture did not decrease. When the methanol had been removed and the solution cooled, the latter was treated with chloroform (5 · 200 ml). The chloroform solution was washed with 5% sodium carbonate solution and water and evaporated in vacuum at 40°. There remained 72 g of a yellowish mass, which was similar to rosin in consistency.

III. Isolation of schizandrin, γ-schizandrin, and schizandrol. The unhydrolyzed fraction of the oil (72 g) was chromatographed on 1.5 kg of alumina in a column 9 cm in diameter. Data on the chromatographic separation are given in Table 1.

TABLE 2. Chromatography of Fractions 5 and 6 on Alumina

Fraction No.	Solvent	Volumes (liter)	Residue (g)	Composition according to paper chromatography data
5.6a	Benzene – ligroin (1 : 1)	1	0.5	γ- and δ-Schizandrins
5.6b	Benzene – ligroin (1 : 1)	1	0.4	γ- and δ-Schizandrins
5.6c	Benzene	2	0.6	δ-Schizandrin and schizandrin
5.6d	Benzene – chloroform (1 : 1)	1	0.4	δ-Schizandrin and schizandrin
5.6e	Chloroform	3	9.4	Schizandrin
5.6f	Methanol	1	0.7	Schizandrin and ε-schizandrin

TABLE 3. Chromatography of Fractions 7 and 8 on Alumina

Fraction No.	Solvent	Volumes (liter)	Residue (g)	Composition according to paper chromatography data
7.8a	Benzene – chloroform (1 : 2)	0.6	1.2	Schizandrin, traces of δ-schizandrin
7.8b	Benzene – chloroform (1 : 3)	1.5	5.1	Schizandrin
7.8c	Benzene – chloroform (1 : 4)	1.5	2.9	Schizandrin
7.8d	Benzene – chloroform (1 : 4)	1.5	6.5	Schizandrin, ε-schizandrin
7.8e	Benzene – chloroform (1 : 4)	1.5	0.6	Schizandrin, ε-schizandrin
7.8f	Methanol	0.6	0.8	Schizandrol

Fractions 3 and 4 were combined and dissolved in 75 ml of n-hexane. Over a period of a month there crystallized 1.8 g of γ-schizandrin with m.p. 92-93° (from hexane or methanol) and $[\alpha]_D$ 0 ± 3° (c 0.15, chloroform). The infrared spectrum is given in Fig. 3.

Ultraviolet spectrum: λ_{max} 220.5 (log ε 4.598), 254 (log ε 4.087) and 282 mμ (log ε 3.509).

Found %: C 69.34, 69.47; H 7.20, 7.12; OCH_3 21.81, 21.59, 21.57. $C_{24}H_{30}O_6$. Calculated %: C 69.54; H 7.27; 3 OCH_3 22.50. $C_{23}H_{28}O_6$. Calculated %: C 68.98; H 7.04; 3 OCH_3 23.23.

Fraction 6 was recrystallized from ether at −60°. We obtained 2.6 g of schizandrin. The vitreous residue obtained after evaporation of the mother solution was combined with fraction 5 and chromatographed on 600 g of alumina in a column 6.5 cm in diameter. The results of chromatography are given in Table 2.

Fraction 5.6e was recrystallized from ether at −60° to yield 5.1 g of schizandrin with m.p. 128-129°, $[\alpha]_D$ + + 91.5° (c 0.1, alcohol), $[\alpha]_D$ + 78° (c 0.1, chloroform). The infrared spectrum is given in Fig. 3.

Ultraviolet spectrum: λ_{max} (log ε 4.530), 251 (log ε 4.141) and an inflection at 280-285 mμ (log ε ~ 3.46).

Found %: C 65.64, 65.42; H 7.56, 7.65; OCH_3 35.94, 35.72; act. H 3.97, 4.10. M 405.4 (cryoscopically in benzene). $C_{23}H_{32}O_7$. Calculated %: C 65.69; H 7.67; 5 OCH_3 36.90; act. H 4.10. M 420.49.

Evaporation of the ether mother solutions yielded an amorphous mass, which contained only traces of schizandrin and whose composition and properties were not investigated.

Fractions 7 and 8 were combined and chromatographed on 800 g of alumina in a column 6.5 cm in diameter. The results of the separation are given in Table 3.

Fractions 7.8a, 7.8b, and 7.8c were recrystallized from ether at −60°. We obtained 3.8 g of schizandrin.

Fraction 7.8f was recrystallized from methanol. We obtained 0.6 g of schizandrol with m.p. 143-144°, $[\alpha]_D$ + + 50° (c 0.1, chloroform), and $[\alpha]_D$ + 62.5° (c 0.1, acetone). The infrared spectrum is given in Fig. 3.

Ultraviolet spectrum: λ_{max} 224 mμ (log ε 4.505), 249 (log ε 4.136), and an inflection at 280-285 mμ.

Found %: C 64.47, 64.28; H 7.11, 7.20; OCH_3 26.12, 25.91. $C_{21}H_{28}O_7$. Calculated %: C 64.26; H 7.19; 3 OCH_3 23.72.

Fractions 7.8d and 7.8e could not be separated into schizandrin and ε-schinzandrin. Freezing the schizandrin out of an ether solution likewise did not give positive results.

By preparative chromoatography on paper in system I it was possible to separate about 20 mg of the mixture of schizandrin and ε-schizandrin. We obtained about 5 mg of an amorphous substance, which gave the spot corresponding to ε-schizandrin. Methylation of this substance with dimethyl sulfate and alkali did not give positive results: judging by paper chromatography, the ε-schizandrin remained unchanged during methylation.

Fraction 9 was recrystallized from methanol. We obtained 1.73 g of schizandrol with m.p. 143-144°.

IV. Acetylation of schizandrol. To a solution of 200 mg of schizandrol in 5 ml of pyridine was added 5 ml of acetic anhydride and the mixture left at room temperature for a day. The excess of the reagents was removed in vacuum and the oily residue gradually solidified when washed repeatedly with water. The crystals were collected and dried in vacuum over P_2O_5. The yield was 160 mg. After recrystallization from a mixture of m-xylene and isooctane, the substance had m.p. 129.5-130.5°.

Found %: C 63.29, 62.68; H 6.78, 6.72. $C_{25}H_{32}O_9$. Calculated %: C 63.01; H 6.77.

V. Methylation of schizandrol. To a solution of 84 mg of schizandrol in 10 ml of 10% KOH solution was added 1 ml of dimethyl sulfate and the mixture heated on a water bath at 35-45° for 0.5 hr. Then a further 0.5 ml of dimethyl sulfate and 0.5 g of KOH in 5 ml of water were added and the mixture was heated for a further 45 min at 80-90°. The mixture was cooled, the reaction products extracted with benzene, the benzene solution washed with water and dried with Na_2SO_4, and the solvent removed in vacuum. The residue was recrystallized from ether at −60°. The substance and a mixture with authentic schizandrin melted at 128-129°. It had R_f 0.68 (system I). The infrared and ultraviolet spectra were identical with those of schizandrin.

SUMMARY

1. The oil of Schizandra chinensis seeds was extracted successively with ligroin and methanol, the methanol fraction hydrolyzed with alkali, and the unhydrolyzed fraction chromatographed repeatedly on alumina to yield the individual compounds schizandrin, $C_{23}H_{32}O_7$, schizandrol, $C_{21}H_{28}O_7$, γ-schizandrin, $C_{23-24}H_{28-30}O_6$ and it was shown that four other substances that absorb in the ultraviolet were present.

2. It was shown that schizandrin contains an o-methylated pyrogallol nucleus and a tertiary hydroxyl group and no double bond, carbonyl group, or lactone rings.

3. Methylation of schizandrol yielded schizandrin. This demonstrates that schizandrin is di-o-methylschizandrol.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

PYRROLIZIDINE ALKALOIDS

II. STEREOSPECIFIC SYNTHESIS OF D,L-ISORETRONECANOL

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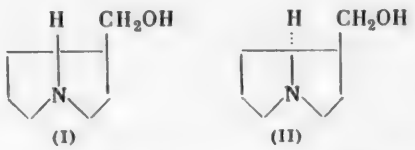
As has now been established, isomeric 1-hydroxymethylpyrrolizidines, which form the basis of some pyrrolizidine alkaloids, differ in the steric arrangement at the C_1 and C_8 atoms of the pyrrolizidine ring, where the substituents (H and CH_2OH) may occupy the cis-(trachelanthamidine and laburnine, I) or the trans-position (isoretronecanol and lindelophidine, II).

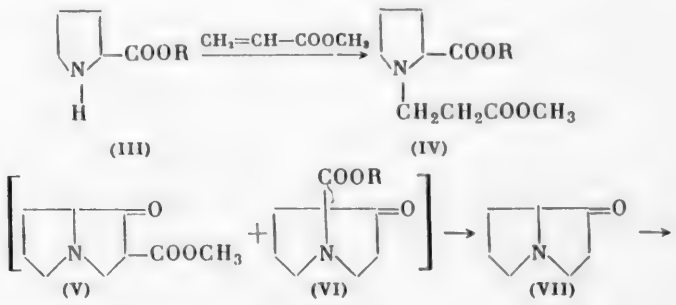


(I) (II)

Although methods have been found for synthesizing 1-hydroxymethylpyrrolizidine, the problem of the stereospecific synthesis of pyrrolizidine amino alcohols cannot be considered solved. By using Leonard's scheme [2], Jezo and Kalac [1] obtained 1-hydroxymethylpyrrolizidine, which was a mixture of the two racemates (I) and (II), with D,L-isoretronecanol (II) predominating. In order to confirm the biogenetic route of the formation of pyrrolizidine alkaloids, Czech chemists [3] synthesized 1-hydroxymethylpyrrolizidine from the bisacetal of γ,γ'-iminodibutyraldehyde, which, according to their data, was D,L-isoretronecanol (II). However, in a recent brief communication [4] it was reported that, on the contrary, cyclization of the bisacetal of γ,γ'-iminodibutyraldehyde at pH 7 gives D,L-trachelanthamidine (I), while cyclization does not occur under the conditions described by the Czech chemists (pH 4.2).

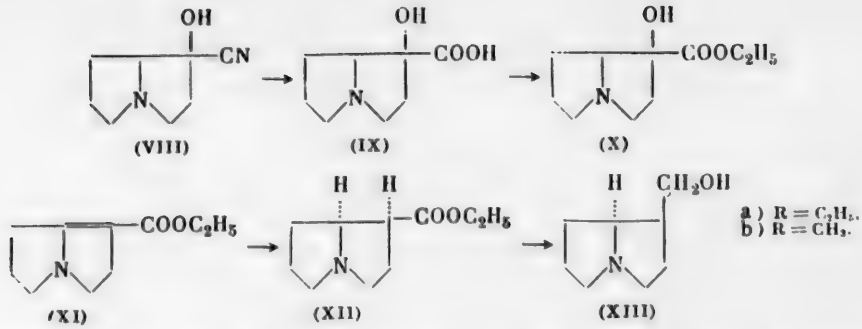
We described two variants of a simple synthesis of D,L-trachelanthamidine [5, 6] and showed that closure of the pyrrolizidine ring from substituted tribromides by a closure procedure proposed in the literature [7] forms, probably for purely energetic reasons, the more stable system of pseudoheliotridane with a cis-configuration at the C_1 and C_8 atoms.

In connection with this, to obtain the heliotridane system, to which isoretronecanol (II) also belongs, another route is required for forming the bicyclic system of 1-hydroxymethylpyrrolizidine. In the present work we developed a scheme which makes possible the stereospecific synthesis of D,L-isoretronecanol.*



(III) (IV) (V) (VI) (VII)

* For a brief communication on this problem, see [8].



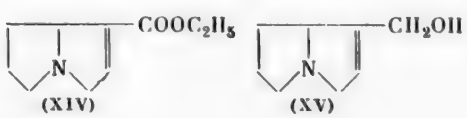
As the starting material we used the ethyl (IIIa) or methyl (IIIb) ester of proline, which was obtained by esterification of proline, synthesized by the method of A. N. Nesmeyanov, R. Kh. Freidlina, and R. G. Petrova [9]. We developed a direct route for the conversion of α,δ-dichlorovaleric acid to proline esters without preliminary isolation of the proline in a pure form. This method made it possible to obtain proline esters in 40-50% yield, calculated on α, δ-dichlorovaleric acid.

By condensation of the proline esters (IIIa and b) with methyl acrylate we obtained methyl β-(N-2-carbethoxypyrrolidine)-propionate (IVa) and methyl β-(N-2-carbomethoxypyrrolidine)-propionate (IVb), respectively [cf. 10].

Metallic potassium and sodium hydride are recommended in the literature [10, 11] as condensing agents for the Dieckmann cyclization of compounds like (IV). We developed a method of cyclization with sodium ethylate. It should be noted that if sodium ethylate completely free from alcohol was used, only traces of the required substance (VII) were obtained, while if a small amount of anhydrous alcohol was added to the reaction mixture, the yield of pyrrolizidone-1 (VII) rose to 55-65%. The cyclization of (IVa and b) could yield two keto esters (Va; VIa, b), but on ketonic cleavage, the two of them should lead to the same ketone. We did not isolate the keto esters in a discrete state and by heating the product of the Dieckmann condensation with 10% hydrochloric acid, we converted them directly into pyrrolizidine-1 (VII). The yield was higher when the ethyl ester (IVa) was used. The reaction of pyrrolizidone-1 (VII) with acetone cyanhydrin gave 1-hydroxy-1-cyanopyrrolizidine (VIII) [cf. 19]. Hydrolysis of the cyanhydrin (VIII) with concentrated hydrochloric acid gave 1-hydroxypyrrolizidine-1-carboxylic acid (IX), which was identified as the hydrochloride or converted into the ethyl ester without isolation in a pure form.

The greatest difficulty was encountered in the next stage of the synthesis, namely, the dehydration of the ester of the hydroxy acid (X). The hydroxy ester (X) was dehydrated in two ways. The first method consisted of treating (X) with thionyl chloride in pyridine and the second, treatment with phosphorus oxychloride in pyridine. In dehydration by the first method, the reaction was difficult to control, was accompanied by considerable tar formation, and was not always reproducible. As a result of this, the yield of the dehydration product was 25-30%. The substance obtained always contained a small amount of a halogen compound, which could not be removed by distillation; it was one of the by-products of the reaction, whose formation was connected with the possible rearrangement of compound (X) is an ester of a β-amino acid and under the action of acid reagents under more or less drastic conditions, rupture of the $C_\beta - N$ bond (β-elimination) may occur with subsequent destruction of the molecule. When the dehydration was carried out with phosphorus oxychloride in pyridine (cf. [13]), the reaction proceeded with much less tar formation and led to the unsaturated ester (XI) in about 50% yield. In contrast to the product from the first method, the dehydration product (XI) did not contain a halogen-containing compound. These differences in the dehydration under the action of different agents may be explained by the fact that during the treatment with thionyl chloride in pyridine there was first replacement of the hydroxyl group by a halogen with subsequent dehydrochlorination and during treatment with phosphorus oxychloride in pyridine, there was direct elimination of water.

The dehydration of (X) could have proceeded in one of two possible directions or in both directions at once and led to (XI), its isomer with the double bond in the 1,2-position (XIV), or a mixture of (XI) and (XIV). The isomer (XIV) would have been of considerable interest as its reduction should have led to the unsaturated pyrrolizidine alcohol supinidine (XV) (cf. [14]).



In connection with this we reduced the dehydration product with lithium aluminum hydride, but the unsaturated alcohol obtained differed in properties from supinidine and corresponded to an enamine; it was oxidized readily in air and gave an unstable picrate, which turned to tar on storage with the liberation of picric acid. On the basis of these data it may be concluded that the dehydration product or at least the bulk of it had the structure (XI). It could be assumed that this would be the preferential direction of the dehydration as it must form the system $>N-CH=CH-CO-$ which is more favored energetically because of the conjugation of the carbonyl group with the free electron pair of the nitrogen atom [15].

For the formation of the heliotridane system, which is present in isoretronecanol, the unsaturated ester (XI) must be reduced with cis-addition of the hydrogen at the double bond (cf. [16]). The most suitable method was found to be catalytic hydrogenation, which was described for a similar system, namely, the conversion of the ethyl ester of Δ'-tetrahydroanthranilic acid into cis-hexahydroanthranilic acid [17]. As a result of the well-known suppression of the double bond in the system $>N-CH=CH-CO-$, the catalytic hydrogenation proceeded slowly and required quite drastic conditions (cf. [15]).

In our case, the compound (XI) was converted to the saturated ester (XII) by hydrogenation in glacial acetic acid over a platinum catalyst 7 atm. It was found that hydrogenation proceeded more readily if a few drops of glacial acetic acid saturated with hydrogen chloride were added to the reaction mixture. This effect may be explained by the formation of the enamine hydrochloride, which is hydrogenated more readily as a result of suppression of conjugation in the system $>N-CH=CH-CO-$. Hydrogenation yielded the ethyl ester of pyrrolizidine-1-carboxylic acid (XII), which gave a picrate with m.p. 118-118.5°. This differs sharply from the melting point of the picrate of the other racemate (m.p. 147-148.5°), which was specially prepared by another method and belongs to the pseudoheliotridane series.* A mixed melting point was strongly depressed.

The final confirmation that the compound we obtained had the configuration of a heliotridane derivative was obtained after the reduction of (XII) to the final synthesis product, namely, 1-hydroxymethylpyrrolizidine, by the action of lithium aluminum hydride in ether. The amino alcohol (XIII), which was obtained in 86% yield, was identified as the picrate with m.p. 186.5-187.5°, which is close to that reported in the literature for D,L-isoretronecanol (190-191°) [1]. The picrate with m.p. 186.5-187.5° was the only picrate which could be isolated from the reaction mixture; the picrate of the other racemate (D, L-trachelanthamidine, m.p. 172-174°) was not isolated. Thus, our synthesis actually gave a stereochemically unequivocal result and led to only one of the two diastereoisomers.

The stereochemical nature of the 1-hydroxymethylpyrrolizidine obtained was demonstrated by comparison of the infrared spectra** of the synthetic amino alcohol, trachelanthamidine, and lindelophidine and by comparison of the infrared spectra of the picrates of these bases; the compounds obtained had spectra which were similar to those of lindelophidine and differed sharply from those of trachelanthamidine (see figure).*** The same result was obtained by comparing the melting point of the picrate of the amino alcohol synthesized with those of the picrate of D,L-trachelanthamidine, which was synthesized previously, and the picrate of D,L-isoretronecanol (m.p. 188.5-189.5°), which was obtained by mixing equal amounts of the picrates of the two antipodal natural pyrrolizidine alcohols. A mixture with the picrate of the amino alcohol we synthesized melted at 187-188.5°; a mixture with trachelanthamidine picrate had a markedly depressed melting point.

All these data indicate that the amino alcohol (XIII) we obtained was D,L-isoretronecanol and a stereospecific synthesis of 1-hydroxymethylpyrrolizidine of the heliotridane series had been achieved.

EXPERIMENTAL

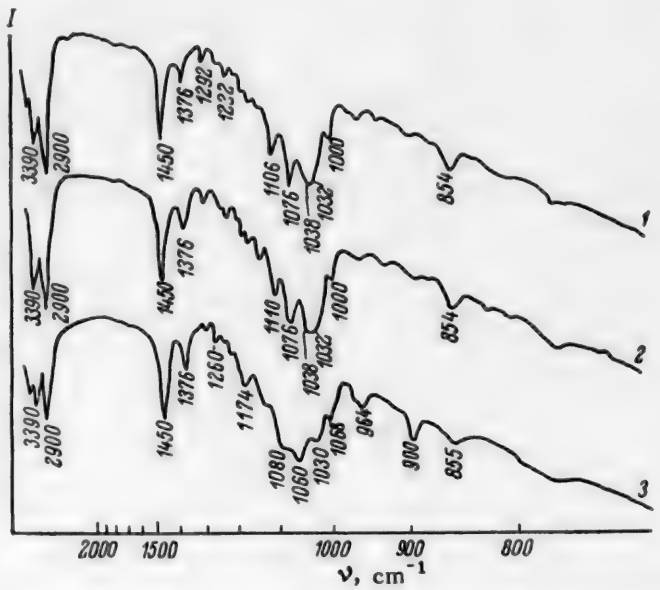
Ethyl ester of proline (IIIa). A solution of 128 g of α,δ-dichlorovaleric acid in 3 ml of 25% ammonia was kept at room temperature for 7 days. The solution was then evaporated to dryness, the residue extracted with 500 ml

* The ethyl ester of pyrrolizidine-1-carboxylic acid of the pseudoheliotridane series was synthesized by the method developed previously for the methyl ester [5].

** The spectral investigations were made by V. G. Vinokurov. The spectra of thin layers were plotted on an IKS-12 instrument with an NaCl prism.

*** In our communication [5], an error was made in the key to the infrared spectra. The infrared spectra of trachelanthamidine, D,L-trachelanthamidine, and lindelophidine were illustrated under the numbers 1, 2, and 3, respectively.

of boiling methanol, the ammonium chloride removed by filtration, and the filtrate evaporated to dryness. The residue was evaporated first with toluene and then with anhydrous alcohol and dissolved in 720 ml of anhydrous alcohol and 85 ml of thionyl chloride added dropwise. The reaction mixture was left at room temperature for 3 days, the alcohol removed, the residue evaporated with dry toluene and dissolved in 250 ml of dry chloroform, and 350 ml



Infrared absorption spectra. 1) Lindelophidine; 2) synthetic 1-hydroxymethylpyrrolizidine; 3) trachelanthamidine.

of dry chloroform saturated with ammonia at 0° added at a temperature of no higher than 0°. The ammonium chloride was removed by filtration, the chloroform evaporated at a temperature of no higher than 20°, and the residue vacuum distilled with a fraction with b.p. 60-62° (3 mm), n^{20}_D 1.4518 collected. The yield of (IIIa) was 56 g (52%, calculated on the α, δ-dichlorovaleric acid).

Literature data [18]: b.p. 78° (12-14 mm).

The methyl ester of proline (IIIb) was obtained by the method described above. It had b.p. 64-66° (8 mm), n^{20}_D 1.4542. The yield was 41 g (42%, calculated on the α, δ-dichlorovaleric acid).

Literature data [19]: b.p. 70° (10 mm).

Methyl β-(N-2-carbethoxypyrrolidine)-propionate (IVa). A mixture of 28 g of the ethyl ester of proline and 56 ml of methyl acrylate, containing traces of hydroquinone, was boiled under reflux for 24 hr. The excess acrylate was removed and the residue vacuum distilled to give a fraction with b.p. 103-106° (1.5-2 mm). The yield was 33 g (74%). After redistillation, the substance had b.p. 92-94° (1 mm), d_4^{20} 1.0818, n^{20}_D 1.4571.

Found %: C 57.78, 57.97; H 8.31, 8.40; N 6.08, 6.12. $C_{11}H_{19}O_4N$. Calculated %: C 57.58; H 8.39; N 6.11.

The picrate was obtained by mixing ether solutions of the base and picric acid. There first precipitated an oily picrate, which crystallized after rubbing. It had m.p. 74.5-75.5° (from alcohol).

Found %: N 12.33, 12.14. $C_{17}H_{22}O_{11}N_4$. Calculated %: N 12.22.

Methyl β-(N-2-carbomethoxypyrrolidine)-propionate (IVb). This was obtained analogously. The yield was 81% and the product had b.p. 86-87° (0.8-1 mm), d_4^{20} 1.1088, n^{20}_D 1.4598.

Found %: C 55.96, 55.80; H 8.36, 8.12; N 6.50, 6.30. $C_{10}H_{17}O_4N$. Calculated %: C 55.80; H 7.96; N 6.50.

The picrate was obtained analogously and had m.p. 78-79°.

Found %: N 12.64, 12.60. $C_{16}H_{20}O_{11}N_4$. Calculated %: N 12.61.

Pyrrolizidone-1 (VII). To alcohol-free sodium ethylate (obtained from 1.7 g of metallic sodium) were added 4.1 ml of anhydrous alcohol, 50 ml of anhydrous xylene, and 16 g of methyl β-(N-2-carbethoxypyrrolidine)-propionate (IVa). When the whole of the sodium ethylate and dissolved, the reaction mixture was heated on an oil bath (150-160°) for 1.5 hr. After the mixture had been cooled, the reaction product was extracted with water (4 · 15 ml). To the combined aqueous extracts was added 40 ml of concentrated hydrochloric acid and the solution obtained heated under reflux on a boiling water bath for 3 hr. The reaction mixture was evaporated, the red residue dissolved in 20 ml of cold water, and the solution saturated with potassium carbonate with cooling and carefully extracted with ether. After removal of the ether, the product was evaporated with dry benzene and vacuum distilled in a nitrogen atmosphere. The pyrrolizidone-1 was obtained as a colorless, mobile liquid, which rapidly darkened in air. The yield was 5.65 g (65%, calculated on IVa).

B.p. 55-56° (3 mm), d_4^{20} 1.0754, $n^{20}D$ 1.4884.

Found %: N 11.49. $C_7H_{11}ON$. Calculated %: N 11.19.

In the cyclization of (IVb) under the same conditions, the yield of pyrrolizidone-1 was 55%.

The picrate was prepared in anhydrous ether. After recrystallization from anhydrous alcohol, the yellow needles had m.p. 162-164° (decompn.).

Found %: C 44.04, 43.98; H 4.17, 4.12. $C_{13}H_{14}O_8N_4$. Calculated %: C 44.06; H 3.98.

1-Hydroxy-1-cyanopyrrolizidine (VIII). With thorough cooling, 7.8 ml of acetone cyanhydrin was added to 8.9 g of pyrrolizidone-1. The reaction mixture was stirred well and left overnight. The pyrrolizidone cyanhydrin precipitated as a white crystalline substance. The acetone formed was removed in vacuum, the residue kept for 3 hr, and then the cyanhydrin collected and washed carefully with dry ether. The yield was 9.85 g (91%); the colorless crystals had m.p. 90-93° (from ethyl acetate).

Found %: C 63.38, 63.32; H 8.00, 8.02. $C_8H_{12}ON_2$. Calculated %: C 63.13; H 7.95.

1-Hydroxypyrrolizidine-1-carboxylic acid (IX). A mixture of 3.05 g of 1-hydroxy-1-cyanopyrrolizidine and 10 ml of concentrated hydrochloric acid was heated on a boiling water bath for 15 hr. The ammonium chloride was removed and washed with cold, concentrated hydrochloric acid, the filtrate evaporated to dryness, the crystalline residue dissolved in a small amount of water, and the solution made alkaline with 40% sodium hydroxide solution. The solution obtained was heated until the evolution of ammonia ceased, acidified with hydrochloric acid, and again evaporated to dryness. The residue crystallized after trituration with dry acetone and was extracted with hot anhydrous alcohol. On cooling, the alcohol solution deposited 1-hydroxypyrrolizidine-1-carboxylic acid hydrochloride. After repeating the operation several times, we obtained 2.8 g (67%) of a colorless crystalline substance with m.p. 165.5-167°.

Found %: N 6.38, 6.53; Cl 17.20, 17.18. $C_8H_{14}O_3NCl$. Calculated %: N 6.74; Cl 17.03.

Ethyl 1-hydroxypyrrolizidine-1-carboxylate (X). A mixture of 8.5 g of 1-hydroxy-1-cyanopyrrolizidine and 25 ml of concentrated hydrochloric acid was heated on a boiling water bath for 15 hr. The reaction mixture was evaporated to dryness, the residue evaporated twice with anhyrdrous alcohol and dissolved in 50 ml of anhydrous alcohol, and the solution obtained saturated with dry hydrogen chloride. The reaction mixture was boiled for 5 hr, the ammonium chloride removed by filtration, the filtrate evaporated, the residue dissolved in 50 ml of anhydrous alcohol, and the solution saturated with dry hydrogen chloride and boiled for 5 hr. The reaction mixture was evaporated, the residue dissolved in 15 ml of water, and the solution made alkaline with potassium carbonate and extracted with ether. The ether extracts were dried with magnesium sulfate, the ether was removed, and the residue crystallized. We obtained 8 g (72%) of a colorless crystalline substance with m.p. 71-72° (from acetone).

Found %: C 60.54, 60.72; H 8.55, 8.48; N 7.08, 6.89. $C_{10}H_{17}O_3N$. Calculated %: C 60.28; H 8.58; N 7.03.

Ethyl $\Delta^{1,8}$-dehydropyrrolizidine-1-carboxylate (XI). a) The oily hydrochloride of the hydroxy ester obtained from 5.3 g of the hydroxy ester (X) was dissolved in 18 ml of dry pyridine and 6 g of thionyl chloride was added dropwise with cooling on an ice bath and vigorous stirring. The reaction mixture was heated carefully on a water bath. When the bath temperature reached 65°, a vigorous reaction began and was accompanied by heat evolution and strong tar formation. The reaction mixture was heated for a further 10 min at a bath temperature of 75-80°, then diluted with 50 ml of dry chloroform, and evaporated. The dark residue was dissolved in 20 ml of water and the solution

made alkaline with potassium carbonate with cooling. The product was extracted carefully with ether, the ether extracts were evaporated, and the residue was evaporated with benzene and vacuum distilled to give a fraction with b.p. 80-90° (2 mm). Redistillation yielded 1.5 g (31%) of an unsaturated ester with b.p. 78-82° (2 mm), n^{20}_D 1.4890, which, according to analysis data, contained a small amount of a halogen-containing compound.

b) To the distillate obtained by distilling a mixture of 50 ml of anhydrous pyridine and 7.8 g of phosphorus oxychloride were added 5 g of the hydroxy ester (X) and 2.8 ml of phosphorus oxychloride with cooling. The reaction mixture was stirred at room temperature for 20 min, then gradually heated to 120° and kept at 120-125° (oil bath) for 30 min. The reaction mixture was evaporated to dryness, the dark residue decomposed by the addition of 10 ml of water with thorough cooling and made alkaline with potassium carbonate, and the product extracted carefully with ether. After removal of the ether, the residue was evaporated with dry benzene and vacuum distilled to give a fraction with b.p. 79-86° (2 mm). Redistillation yielded 2.2 g (48%) of a colorless mobile liquid with b.p. 79-81° (2 mm), n^{20}_D 1.4885. The substance obtained readily decolorized an acid solution of potassium permanganate and was oxidized rapidly in air.

Found %: N 7.61, 7.58. $C_{10}H_{15}O_2N$. Calculated %: N 7.72.

The picrate was obtained by mixing ether solutions of the base and picric acid. After three recrystallizations from anhydrous alcohol, the yellow needles had m.p. 154-155.5°.

Found %: C 46.76, 46.71; H 4.66, 4.66; N 13.58, 13.44. $C_{16}H_{18}O_9N_4$. Calculated %: C 46.83; H 4.42; N 13.65.

Ethyl pyrrolizidine-1-carboxylate (XII). A 4 g sample of the unsaturated ester (XI) in 25 ml of glacial acetic acid to which had been added a few drops of acetic acid saturated with hydrogen chloride was hydrogenated at room temperature and 7 atm over 0.1 g of platinum oxide. The required amount of hydrogen was absorbed in 2 hr. The catalyst was removed by filtration, the acetic acid evaporated, the residue dissolved in 5 ml of cold water and acidified with 2 N hydrochloric acid, and the "nonbasic" impurities were extracted several times with ether. The aqueous solution was made alkaline with potassium carbonate with thorough cooling and extracted repeatedly with ether. The ether was evaporated and the residue evaporated with dry benzene and vacuum distilled to give a fraction with b.p. 73-74° (1.5 mm). The yield was 3.07 g (76%). Redistillation yielded a colorless mobile liquid. The substance did not decolorize an acid solution of potassium permanganate.

B.p. 79-80° (2 mm), d_4^{20} 1.0515, n^{20}_D 1.4715.

Found %: N 7.56, 7.41. $C_{10}H_{17}O_2N$. Calculated %: N 7.64.

The picrate was obtained by mixing alcohol solutions of the base and picric acid. The yellow needles had m.p. 118-118.5° (from alcohol).

Found %: C 46.81, 46.86; H 4.90, 5.03. $C_{16}H_{20}O_9N_4$. Calculated %: C 46.60; H 4.89.

Literature data for ethyl ester of isoretronecanolic acid [20]: b.p. 82-83° (2 mm), d_4^{20} 1.0465, n^{20}_D 1.4715. Picrate, m.p. 112-113°.

1-Hydroxymethylpyrrolizidine (D,L-isoretronecanol (XIII). A solution of 1.5 g of ethyl pyrrolizidine-1-carboxylate in 75 ml of ether was added dropwise with stirring to a solution of 0.75 g of lithium aluminum hydride in 25 ml of ether. The reaction mixture was boiled for 1.5 hr and then decomposed with thorough cooling by the successive addition of 1 ml of water, 0.5 ml of 20% sodium hydroxide, 2.8 ml of water, and 3.2 ml of 40% sodium hydroxide and the product extracted carefully with ether. The extracts were dried over potassium carbonate, the ether was removed, and the residue vacuum distilled to give a fraction with b.p. 108-110° (2.5 mm), n^{20}_D 1.4996 . The yield was 1 g (86%).

Found %: N 9.85, 9.84. $C_8H_{15}ON$. Calculated %: N 9.93.

The picrate was obtained by mixing ether solutions of the base and picric acid. The yellow needles had m.p. 186.5-187.5° (from alcohol).

Found %: C 45.42, 45.20; H 4.77, 4.88. $C_{14}H_{18}O_8N$. Calculated %: C 45.41. H 4.90.

Literature data [1]: b.p. 141-144° (9 mm), n^{20}_D 1.4975. Picrate, m.p. 190-191°.

SUMMARY

A stereospecific synthesis of D,L-isoretronecanol was developed.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

DERIVATIVES OF 1-AZABICYCLO-(3,2,1)-OCTANE ANALOGOUS TO QUININE ALKALOIDS

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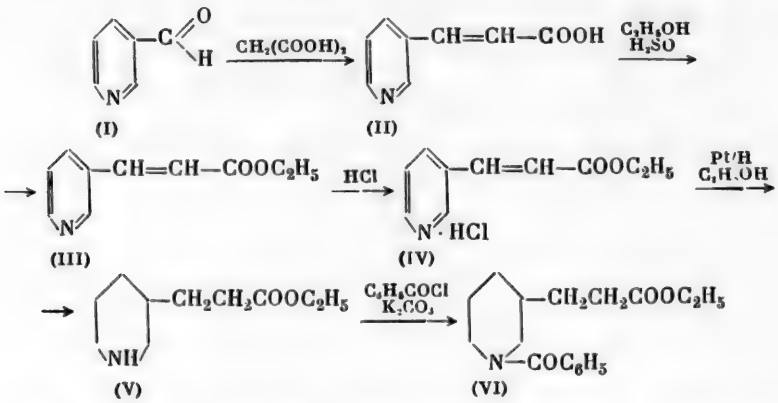
Among the analogs of quinine alkaloids, compounds containing the isomeric 1-azabicyclo-(3,2,1)-octane nucleus instead of the nucleus of the azabicyclic system of quinuclidine have remained unknown up to now. We undertook the synthesis of such compounds for studying their biological activity, in particular, their antimalarial action. During the investigation of 7-monosubstituted 1-azabicyclo-(3,2,1)-octanes [1, 2], we obtained as mixtures of the diastereoisomers [1-azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol (XII) and [4-methyl-1-azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol (XXVIII).

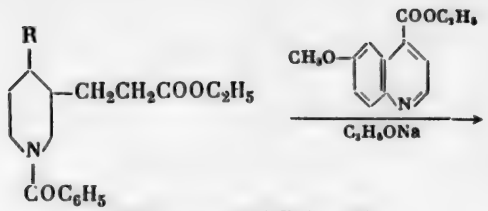
The starting material for the synthesis of (XII) was N-benzoyl-3-(β-carbethoxyethyl)-piperidine (VI), which was synthesized from nicotinic aldehyde by the following scheme:



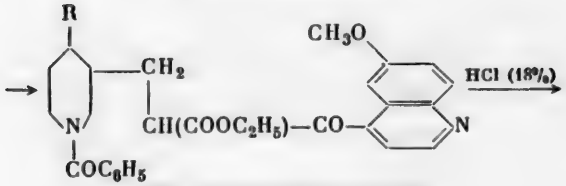
The hydrochloride (IV) obtained from ethyl pyridyl-3-acetylate [3] (III) was hydrogenated over Adams' catalyst to the hydrochloride of ethyl piperidyl-3-propionate, which was converted into the base (V) that was identical with the base obtained by Prelog et al. [4]. Benzoylation of (V) gave an almost quantitative yield of N-benzoyl-3-(β-carbethoxyethyl)-piperidine (VI).

[1-Azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol (XII) was synthesized by a scheme analogous to that used previously for the synthesis of quinuclidyl-2-arylcarbinols [5].

N-Benzoyl-3-(β-carbethoxyethyl)-piperidine (VI) was condensed by Claisen's method with ethyl quininate in the presence of sodium ethylate in xylene. The ester (VII) formed was hydrolyzed with hydrochloric acid (with simultaneous elimination of the benzoyl group) into β-(piperidyl-3)-ethyl 6'-methoxyquinolyl-4' ketone dihydrochloride (VIII). By treatment with sodium hydroxide, the dihydrochloride (VIII) was converted into the base (IX), which was then converted into the corresponding dihydrobromide with subsequent bromination to form β-(piperidyl-3)-α-bromoethyl 6'-methoxyquinolyl-4' ketone dihydrobromide (X). When treated with sodium carbonate solution, the bromo derivative (X) underwent cyclization to form [1-azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4') ketone (XI). Hydrogenation of (XI) in the presence of palladium chloride in hydrochloric acid and subsequent treatment with a solution of sodium hydroxide yielded [1-azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol (XII).



(VI) R = H; (XXII) R = CH_3.



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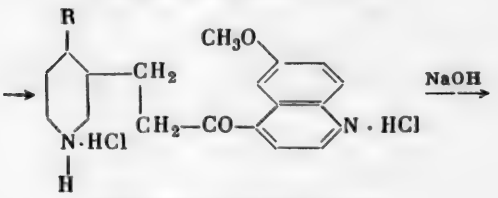
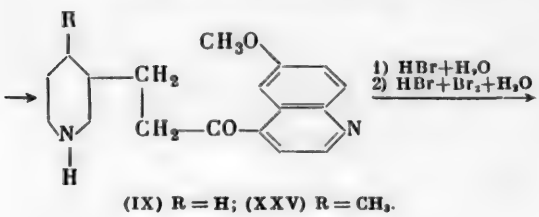
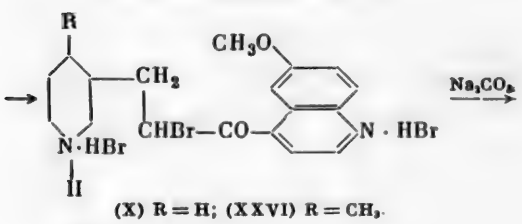


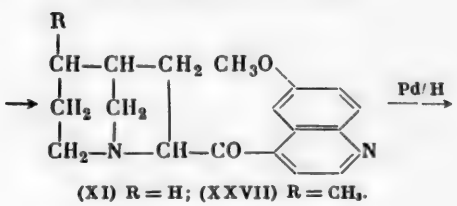
(VIII) R = H; (XXIV) R = CH_3.



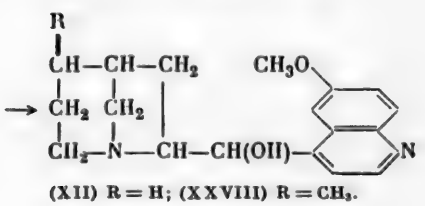
(IX) R = H; (XXV) R = CH_3.



(X) R = H; (XXVI) R = CH_3.

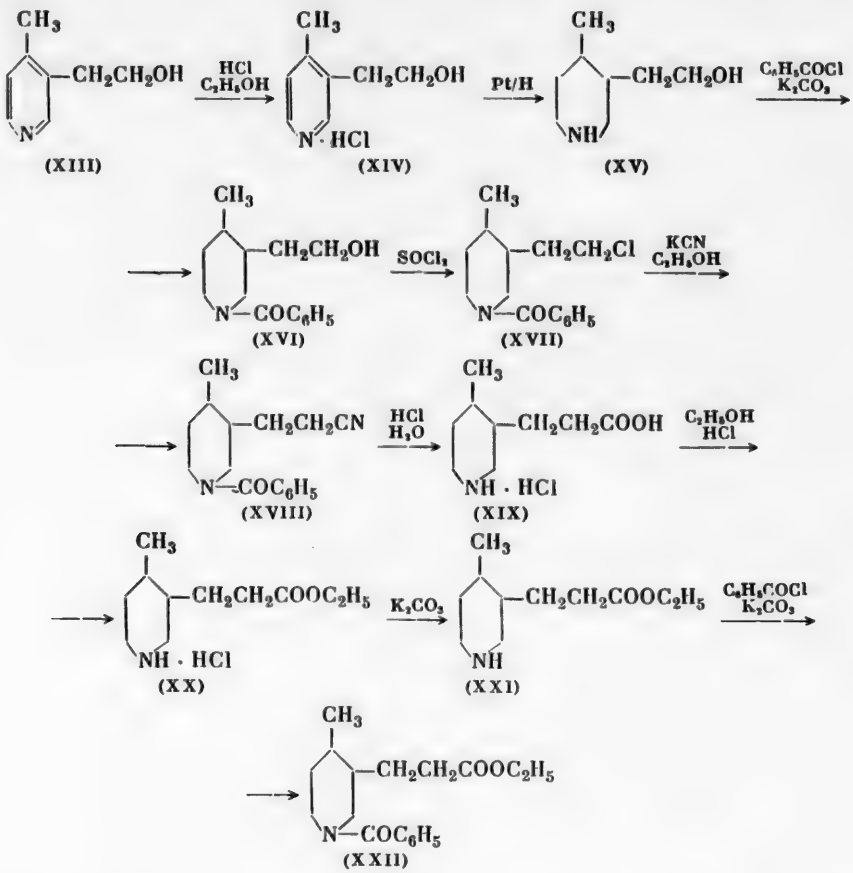


(XI) R = H; (XXVII) R = CH_3.



(XII) R = H; (XXVIII) R = CH_3.

As the starting material for the synthesis of the carbinol (XXVIII), we prepared N-benzoyl-3-(β-carbethoxyethyl)-4-methylpiperidine (XXII) from 3-(β-hydroxyethyl)-4-methylpyridine [6] according to the following scheme:



(XIII) (XIV) (XV) (XVI) (XVII) (XVIII) (XIX) (XX) (XXI) (XXII)

The hydrochloride (XIV) obtained from 3-(β-hydroxyethyl)-4-methylpyridine (XIII) was hydrogenated over Adams' catalyst to 3-(β-hydroxyethyl)-4-methylpiperidine hydrochloride, which was then converted into the base (XV). 3-(β-Hydroxyethyl)-4-methylpiperidine (XV) was benzoylated to N-benzoyl-3-(β-hydroxyethyl)-4-methylpiperidine (XVI). Treatment of the N-benzoyl derivative with thionyl chloride yielded N-benzoyl-3-(β-chloroethyl)-4-methylpiperidine (XVII). The latter was treated with potassium cyanide in alcohol to form N-benzoyl-3-(β-cyanoethyl)-4-methylpiperidine (XVIII), which was converted by prolonged boiling with concentrated hydrochloric acid into β-(4-methylpiperidine-3)-propionic acid hydrochloride (XIX). The acid hydrochloride (XIX) was esterified to ethyl β-(4-methylpiperidyl-3)-propionate hydrochloride (XX), which was then converted into the base (XXI), benzoylation of which gave N-benzoyl-3-(β-carbethoxyethyl)-4-methylpiperidine (XXII).

The carbinol (XXVIII) was obtained analogously to the carbinol (XII) by the scheme given above. During the course of the synthesis we isolated β-(4-methylpiperidyl-3)-ethyl 6'-methoxyquinolyl-4' ketone (XXV) and 4-methyl-1-azabicyclo-(3,2,1)-octyl-7 6'-methoxyquinolyl-4' ketone (XXVII). By hydrogenation over palladium chloride in hydrochloric acid, the ketone (XXVII) was converted into the hydrochloride, which was then converted into the base [4-methyl-1-azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol (XXVIII). Compounds (XXV), (XXVII), and (XXVIII) were identified as the dipicrates.

A chemotherapeutic study of the carbinols (XII) and (XXVIII), which was carried out in our institute by N. A. Novitskaya on chicks infected with Plasmodium gallinaceum, showed that these compounds are inactive and more toxic than quinine. The separation of the mixtures of diastereoisomers (XII) and (XXVIII) for the isolation of more active compounds was therefore unprofitable.

EXPERIMENTAL

Ethyl β-(piperidyl-3)-propionate (V). A 13.4 g sample of ethyl (pyridyl-3)-acrylate hydrochloride (IV), which was obtained from the corresponding base [3], was hydrogenated over 0.8 g of Adams' catalyst in 200 ml of anhydrous alcohol at room temperature and a hydrogen pressure of 70-80 cm of water. After the absorption of 6200 ml of hydrogen, the alcohol solution was filtered to remove the catalyst and evaporated in vacuum, the residue treated with a 50% aqueous solution of potassium carbonate, and the base (V) isolated by extraction with ether. The extract was dried with potassium carbonate, the ether evaporated in vacuum, and the residue vacuum distilled. The yield of (V) was 10.4 g (90%). It had b.p. 119° (6.5 mm) and n^{20}_D 1.4635.

Found %: N 7.63. $C_{10}H_{19}O_2N$. Calculated %: N 7.57.

N-Benzoyl-3-(β-carbethoxy)-piperidine (VI). A solution of 9.6 g of benzoyl chloride in 15 ml of dry chloroform was added dropwise over a period of 10 min at room temperature with stirring to a mixture of 9.2 g of the ester (V), 11 g of powdered, baked potassium carbonate, and 130 ml of dry chloroform. The mixture was stirred at room temperature for 15 min, 5.3 ml of water added, the mixture stirred at room temperature for 3 hr and at 65° on a water bath for 1 hr and filtered, and the residue washed with chloroform. The filtrate was dried with potassium carbonate and evaporated in vacuum and the residue vacuum distilled. The yield was 14.5 g (quantitative). The colorless oil was soluble in chloroform, alcohol, and acetone. It had b.p. 186° (0.15 mm).

Found %: C 70.38, 70.24; H 7.70, 7.92; N 4.58. $C_{17}H_{23}O_3N$. Calculated %: C 70.57; H 8.01; N 4.84.

β-(Piperidyl-3)-ethyl 6'-methoxyquinolyl-4' ketone (VIII). A 2.9 g portion of sodium was reduced to powder by mechanical stirring in 15 ml of boiling xylene and 8.1 g of anhydrous alcohol and 8.1 ml of xylene. The mixture was stirred at 85-90° for 3.5 hr. When the mixture had been cooled to room temperature, 20.1 g of ethyl quininate, 14 g of the piperidine (VI), and 11 ml of dry xylene were added. The reaction mixture was stirred for 7 hr at 87-90° (vaseline bath) and cooled, 240 ml of 18% hydrochloric acid added, the xylene layer separated, the aqueous layer filtered, and the filtrate heated at 110-120° for 4 hr. The cooled solution was extracted with ether to remove benzoic acid and then 112 ml of 40% sodium hydroxide solution added to the aqueous layer with cooling. The liberated oil was extracted with ether, the extract dried with potassium carbonate, and the ether evaporated in vacuum. The yield was 7.9 g [53.6%, calculated on (VI)]. The reddish brown oil was readily soluble in ether and mineral acids.

The dipicrate formed yellow crystals with m.p. 64-68° (decomp.) (from alcohol).

Found %: C 47.32, 47.75; H 3.60, 3.96; N 14.60. $C_{18}H_{22}O_2N_2 \cdot 2C_6H_3O_7N_3$. Calculated %: C 47.65; H 3.73; N 14.82.

1-Azabicyclo-(3,2,1)-octyl-7 6'-methoxyquinolyl-4' ketone (XI). A 7.6 g sample of the ketone (VIII) was dissolved in the cold in 42 ml of 47.5% hydrobromic acid and a solution of 4.1 g of bromine in 27 ml of 47.5% hydrobromic acid added over a period of 25 min with stirring at 70°. The temperature of the mixture was then raised to 80° and stirring continued for 40 min. The solution obtained was evaporated in vacuum at 50°. The residue was dissolved in 34 ml of water and 115 ml of benzene and 340 ml of a 10% sodium carbonate solution were added to the solution. The mixture was shaken for 24 hr, the benzene layer separated, and the aqueous layer further extracted with benzene. The benzene solution was dried with potassium carbonate and evaporated in vacuum at 50°. The yield was 5.6 g [74.9%, calculated on (VI), and 40.1% calculated on (VIII)]. The spongy brown mass had an indefinite melting point (about 65°).

Found %: N 9.36. $C_{18}H_{20}O_2N_2$. Calculated %: N 9.45.

The dipicrate formed yellow crystals with m.p. 140° (decomp.).

Found %: N 14.75. $C_{18}H_{20}O_2N_2 \cdot 2C_6H_3O_7N_3$. Calculated %: N 14.86.

[1-Azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol (XII). A mixture of 1.2 g of the ketone (XI), 14.9 ml of 1 N hydrochloric acid, and 1.6 ml of 2% palladium chloride solution was shaken in a hydrogenation bottle at a hydrogen pressure of 70-80 cm of water and 20° for 25 hr. The catalyst was removed by filtration and washed several times with distilled water. To the aqueous filtrate was added 40% aqueous sodium hydroxide solution (to an alkaline reaction to phenolphthalein) and the liberated oil extracted with chloroform. The chloroform extract was dried over potassium carbonate and evaporated in vacuum at 40-50°; the residue was kept at 0.3 mm for 15 min. The yield was 0.7 g (58.8%). The light yellow powder had m.p. 60-62° and was soluble in chloroform and insoluble in benzene.

Found %: N 7.97. $C_{19}H_{22}O_2N_2$. Calculated %: N 7.43.

The dipicrate was an amorphous powder.

Found %: C 47.66; H 3.79. $C_{19}H_{22}O_2N_2 \cdot 2C_6H_3O_7N_3$. Calculated %: C 47.65; H 3.73.

3-(β-Hydroxyethyl)-4-methylpyridine hydrochloride (XIV). A 50.3 g sample of 3-(β-hydroxyethyl)-4-methylpyridine [6] (XIII) was dissolved in the minimal amount of anhydrous alcohol and a 15% solution of hydrogen chloride in anhydrous alcohol added (to an acid reaction to Congo). The hydrochloride (XIV) was then precipitated completely by the addition of absolute ether, collected, and dried in a vacuum desiccator over calcium chloride and sodium hydroxide. The yield was 57.5 g (90.5%). The m.p. was 108-110°. The colorless crystals were readily soluble in water and alcohol and difficultly soluble in ether.

Found %: N 7.92. $C_8H_{11}ON \cdot HCl$. Calculated %: N 8.08.

N-Benzoyl-3-(β-hydroxyethyl)-4-methylpiperidine (XVI). A mixture of 13 g of the hydrochloride (XIV), 0.68 g of platinum oxide (Adams' catalyst), and 180 ml of anhydrous alcohol was shaken with hydrogen at room temperature and a hydrogen pressure of 70-80 cm of water. The hydrogenation proceeded slowly and fresh 0.68 g portions of platinum oxide were added four times during the reaction. When the hydrogenation was complete, the catalyst was removed by filtration, the alcohol solution evaporated in vacuum, a 50% aqueous solution of potassium carbonate added to the residue, and the liberated oil extracted with ether. The extract was dried with potassium carbonate, evaporated in vacuum, and the residue distilled. The yield of 3-(β-hydroxyethyl)-4-methylpiperidine (XV) was 10.6 g (98.4%). The colorless oil had b.p. 111.5-113° (0.5 mm), 139.5-141° (10 mm), and was soluble in ether and chloroform.

A 7.3 g sample of the piperidine (XV) was dissolved in 110 ml of dry chloroform, 11 g of powdered, baked potassium carbonate added, and 7.8 g of benzoyl chloride introduced with stirring. The reaction mixture was stirred at 20° for 4.5 hr, 1.5 ml of water added, and the mixture again stirred at 20° for 12.5 hr and at 65° for 2 hr. The potassium carbonate was removed by filtration and washed with the chloroform and the filtrate dried with potassium carbonate and evaporated in vacuum. The residue after evaporation of the chloroform was vacuum distilled. The yield of (XVI) was 9.8 g [77.8%, calculated on (XV)] and the product had b.p. 227-229° (0.25 mm), $n^{18}D$ 1.5537. The colorless, viscous oil was soluble in chloroform.

Found %: C 72.85; H 8.58; N 5.55. $C_{15}H_{21}O_2N$. Calculated %: C 72.90; H 8.50; N 5.65.

N-Benzoyl-3-(β-cyanoethyl)-4-methylpiperidine (XVIII). A 30.8 g sample of the piperidine (XVI) was dissolved in 85 ml of dry chloroform and heated with 88 ml of thionyl chloride at 70° for 5 hr. The excess thionyl chloride and chloroform were then removed in vacuum at 50°. For purification, the piperidine (XVII) was evaporated five times successively with benzene (50 ml portions), dissolved in chloroform, and washed with a 10% aqueous solution of sodium bicarbonate (to pH 7 to litmus), the chloroform solution dried with sodium sulfate and evaporated in vacuum, the residue dissolved in ligroin with b.p. 80-100° and treated with activated charcoal, the ligroin removed in vacuum, and traces of solvent removed by heating at 50° and 0.5 mm for 20 min. After these operations, we obtained 29.7 g of a light yellow oil with $n^{20}D$ 1.5488 and d_4^{20} 1.1297, [MR_D 74.79 (calculated 74.49)], which was N-benzoyl-3-(β-chloroethyl)-4-methylpiperidine (XVII). The product obtained was mixed with 14.9 g of 98% potassium cyanide and 140 ml of alcohol and the mixture boiled for 65 hr. After the mixture had cooled, the precipitate was removed by filtration and washed several times with alcohol and the filtrate evaporated in vacuum (4-5 mm) at 50°. The residue was extracted with absolute ether. The extract was evaporated in vacuum and the residue vacuum distilled. The yield of (XVIII) was 23.3 g [70.3%, calculated on (XVI)]. The product had b.p. 185-187° (0.2 mm) and $n^{20}D$ 1.5467.

Found %: C 75.04; H 7.90. $C_{16}H_{20}ON_2$. Calculated %: C 74.95; H 7.85.

3-(β-Carbethoxyethyl)-4-methylpiperidine (XX). A mixture of 26.7 g of the piperidine (XVIII) and 450 ml of concentrated hydrochloric acid (d 1.19) was boiled for 51 hr. The benzoic acid was removed by filtration and the filtrate extracted with ether. The aqueous layer was evaporated to dryness in vacuum, the residue dissolved in 410 ml of a 15% solution of hydrogen chloride in anhydrous alcohol, and the solution boiled for 5 hr. The alcohol was removed in vacuum and the residue made alkaline (to phenolphthalein) with a 50% aqueous solution of potassium carbonate and extracted with ether. The extract was dried with potassium carbonate and evaporated in vacuum and the residue distilled. The yield was 11.5 g (55.4%) and the product had b.p. 142-144° (17 mm) and $n^{20}D$ 1.4670. The clear oil with an amine odor was soluble in ether and chloroform.

Found %: C 66.25; H 10.88. $C_{11}H_{21}O_2N$. Calculated %: C 66.35; H 10.04.

N-Benzoyl-3-(β-carbethoxyethyl)-4-methylpiperidine (XXII). A solution of 10.9 g of benzoyl chloride in 15 ml of dry chloroform was added dropwise to a mixture of 11.4 g of the piperidine (XX), 12.5 g of powdered, baked potassium carbonate, and 91 ml of dry chloroform. The mixture was stirred for 15 min, 6 ml of water added, the mixture stirred for 3 hr at room temperature and for 2 hr at 67°, cooled, and filtered, the filtrate dried with potassium carbonate and evaporated in vacuum, and the residue distilled. The yield was 13.2 g (76.5%). The clear viscous oil was soluble in chloroform and had b.p. 168-169° (0.15 mm).

Found %: C 71.02; H 8.07; N 4.71, 4.92. $C_{18}H_{25}O_3N$. Calculated %: C 71.20; H 8.31; N 4.62.

β-(4-Methylpiperidyl-3)-ethyl 6'-methoxyquinolyl-4' ketone (XXV). A 3.8 g portion of metallic sodium was suspended in boiling xylene with stirring the suspension cooled, and a mixture of 11 ml of anhydrous alcohol and 11 ml of dry xylene gradually added with stirring; the mixture was then stirred for 1 hr at 85-90°. To the sodium ethylate formed were added 15.1 g of the piperidine (XXII), 16.9 g of ethyl quininate, and 10 ml of xylene. The mixture was stirred at 90° for 5.5 hr and left at 20° for 12 hr. Then after it had been checked that no metallic sodium remained unreacted, 312 ml of 18% hydrochloric acid was added with cooling, the xylene layer separated, and the aqueous layer heated at 110-120° for 4 hr. The benzoic acid formed was extracted with ether and 157 ml of 40% aqueous sodium hydroxide solution added to the aqueous layer with cooling. When 118.5 ml of the sodium hydroxide solution had been added, at pH < 7 there separated a tarry product, which was soluble in ether and mineral acids, and this was extracted with ether. Further addition of sodium hydroxide (to an alkaline reaction to phenolphthalein) liberated an oil, which was extracted with ether. The ether extract was dried with potassium carbonate and evaporated in vacuum at 40°; we obtained 6.4 g of (XXV). The tarry products liberated at pH < 7 were boiled with 140 ml of 18% hydrochloric acid for 4 hr, the solution cooled and extracted with ether, the aqueous layer treated with sodium hydroxide solution (to an alkaline reaction to phenolphthalein), and the liberated oil extracted with ether. From the ether extract we isolated a further 0.7 g of (XXV). The total yield was 7.1 g [34.9%, calculated on (XXII)]. The reddish brown oil was soluble in ether and alcohol and difficultly soluble in water.

The dipicrate was prepared by adding an alcohol solution of the ketone (XXV) to excess of a 5% solution of picric acid in alcohol. It had m.p. 177.5-179.5° (from alcohol).

Found %: C 48.54, 48.15; H 4.12, 4.12; N 14.60. $C_{19}H_{24}O_2N_2 \cdot 2C_6H_3O_7N_3$. Calculated %: C 48.30; H 3.92; N 14.55.

4-Methyl-1-azabicyclo-(3,2,1)-octyl-7 6'-methoxyquinolyl-4' ketone (XXVII). A 6.9 g sample of the ketone (XXV) was dissolved with cooling in 37 ml of 47.9% hydrobromic acid (d 1.842), the solution heated to 70°, and a solution of 3.6 g of bromine in 23 ml of 47.9% hydrobromic acid added over a period of 45 min with stirring. The reddish brown solution of the hydrobromide (XXVI) was evaporated in vacuum at 50-57°, the residue dissolved in 45 ml of water, 420 ml of 10% sodium carbonate solution and 150 ml of benzene were added, and the mixture was shaken for 17.5 hr. The benzene layer was separated and the aqueous layer extracted repeatedly with benzene. The combined benzene solutions were dried with potassium carbonate and evaporated in vacuum at 35°. The yield was 5.7 g [82.5%, calculated on (XXV)] and the m.p. 60-65° (Kofler block). The product was soluble in benzene, chloroform, alcohol, acetone, and mineral acids and difficultly soluble in ether and water.

Dipicrate. An alcohol solution of the ketone (XXVII) was added to excess of a 5% alcohol solution of picric acid. The picrate had m.p. 124-126°.

Found %: C 48.87, 48.76; H 3.90, 4.00; N 14.70. $C_{19}H_{22}O_2N_2 \cdot 2C_6H_3O_7N_3$. Calculated %: C 48.45; H 3.67; N 14.58.

[4-Methyl-1-azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol (XXVIII). A mixture of 1.2 g of the ketone (XXVII), 31 ml of a 1 N solution of hydrochloric acid, and 3.8 ml of 2% palladium chloride solution was shaken with hydrogen at 20° for 25 hr at a pressure of 70-80 cm of water. The theoretical amount of hydrogen (105 ml of 19.5°) was absorbed during the hydrogenation. The catalyst was removed by filtration and washed several times with water on the filter. To the aqueous filtrate was added a 40% solution of sodium hydroxide (to an alkaline reaction to phenolphthalein). The liberated oil was extracted with chloroform and the extract dried with potassium carbonate and evaporated in vacuum at 40-50°. The yield was 0.9 g (72.9%). The brownish yellow mass, which melted at 57-60°, was readily soluble in alcohol, acetone, and chloroform, moderately soluble in benzene, and difficultly soluble in ether.

Dipicrate. An alcohol solution of the ketone (XXVIII) was added to excess of a 5% alcohol solution of picric acid. The light yellow crystals were readily soluble in acetone, moderately soluble in ethanol, methanol, benzene, and chloroform, and difficultly soluble in water and ether. They had m.p. 115-117°.

Found %: C 48.06; H 3.90; N 14.32. $C_{19}H_{24}O_2N_2 \cdot 2C_6H_3O_7N_3$. Calculated %: C 48.32; H 3.92; N 14.54.

SUMMARY

Compounds analogous to quinine alkaloids, namely, [1-azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol and [4-methyl-1-azabicyclo-(3,2,1)-octyl-7]-(6'-methoxyquinolyl-4')-carbinol, were synthesized in the form of mixtures of diastereoisomers.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

LETTERS TO THE EDITOR

NEW SYNTHESIS OF 5,6-DISUBSTITUTED PYRIDINES

M. P. Shusherina, R. Ya. Levina, and Khuan Khua-min'

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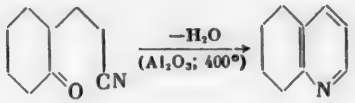
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10
pp. 3477-3478, October, 1961
Original article submitted June 12, 1961

We found a new catalytic reaction for the direct conversion of cyanoethylated ketones into pyridines and pyridones. Thus, passing monocyanoethylated cyclohexanone (2-β-cyanoethylcyclohexanone) over alumina at 400° in a stream of nitrogen in a flow system formed 5,6-cyclohexanopyridine (5,6,7,8-tetrahydroquinoline) in a yield of 20-25%.



The cyclohexanopyridine obtained, which was purified by conversion into the picrate and subsequent decomposition of the latter, had the following constants:

B.p. 98-99° at 10 mm, n^{20}_D 1.5492, d_4^{20} 1.0270.

Found %: C 80.98, 81.28; H 8.74, 8.29. $C_9H_{11}N$. Calculated %: C 81.15; H 8.44.

The picrate had m.p. 157° (from alcohol).

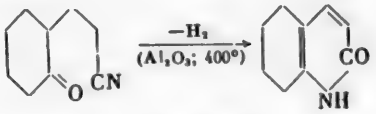
Found %: N 15.66, 15.41. $C_{15}H_{14}O_7N_4$. Calculated %: N 15.47.

The iodomethylate had m.p. 143-145° (from a mixture of alcohol and carbon tetrachloride).

Found %: C 43.63, 43.81; H 5.04, 5.04. $C_{10}H_{14}NI$. Calculated %: C 43.63; H 5.13.

Literature data [1]: b.p. 222° and d_4^{20} 1.0250; picrate, m.p. 157°.

Under the above conditions, 2-β-cyanoethylcyclohexanone formed 5,6-cyclohexanopyridone-2 (~20% yield) together with the 5,6-cyclohexanopyridine.



The cyclohexanopyridone obtained melted at 203-204° (from ethyl acetate). A mixed melting point with authentic cyclohexanopyridone was not depressed. Literature data [2]: m.p. 203-204°.

The investigation of catalytic conversions of ketonitriles is continuing.

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TRITERPENES FROM THE BARK OF QUERCUS PETRAEA LIEBL

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
p. 3478, October, 1961
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From the bark of Quercus petraea we isolated the triterpene ketone friedelin and the alcohol corresponding to it, friedelanol (equatorial isomer). The axial isomer, epifriedelanol has been found in some plants, while friedelanol has been isolated from lignite [1] and the leaves of two forms of Euonymus [2].

The mixture of substances extracted from 6 kg of bark with chloroform was dissolved in 950 ml of benzene and chromatographed on 1.2 kg of alumina of activity II. Elution with benzene yielded successively a noncrystalline substance, friedelin (460 mg), a crystalline substance with m.p. 69-70° (80 mg), friedelanol (700 mg), and an unseparable mixture of crystalline substances (300 mg). The triterpenes were recrystallized from a mixture of chloroform with methanol or ethanol. For comparison, we prepared friedelanol from a sample of authentic friedelin by reduction with sodium in amyl alcohol. The data on the identification of the substances are given in the table.

Substance	M. p.	Found %		Empirical formula	Calc. %		Literature date [3]
		C	H		C	H	
Friedelin	262—4° $[\alpha]_D$ +27°	84.76	12.00	$C_{30}H_{50}O$	84.67	12.03	264—265° $[\alpha]_D$ +28°
Friedelin oxime	285—7	—	—	—	—	—	290—294
Friedelanol	302—5	84.01, 84.17	12.27, 12.23	$C_{30}H_{52}O$	84.04	12.22	301—304
Friedelanol acetate	316—7	—	—	—	—	—	315—316

The infrared spectra of friedelin and friedelanol in the region of 1800-800 cm^{-1} were identical with the spectra of authentic samples. The substances were also identified by mixed melting points.

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REACTION OF DICYCLOPROPYL KETONE WITH ALKYLMAGNESIUM BROMIDES AND SYNTHESIS OF 1,1-DICYCLOPROPYL-1,3-BUTADIENE

I. A. D'yakonov, S. Kh. Begidov, and T. V. Domareva

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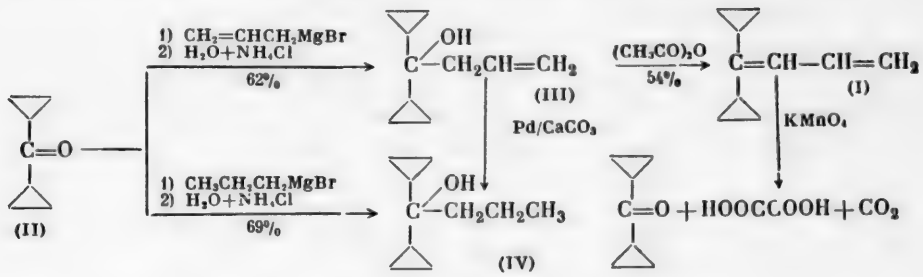
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
p. 3479, October, 1961
Original article submitted June 24, 1961

Only two homologs of 1,3-butadiene containing cyclopropyl radicals have been known up to now, namely, 2-cyclopropyl-1,3-butadiene [1] and 1-(2,2-dichlorocyclopropyl)-1,3-butadiene [2].

In the present letter we report the synthesis of a disubstituted representative of this series, namely, 1,1-dicyclopropyl-1,3-butadiene (I) from dicyclopropyl ketone (II) [3] and allylmagnesium bromide.



B.p. 68-70° at 11 mm, d_4^{20} 0.9106, n^{20}_D 1.5012, MR_D 43.43; calc. 44.46.

Found %: C 89.01; H 10.84. $C_{10}H_{14}$. Calculated %: C 89.41; H 10.52.

It changed slowly during storage. The substance partly polymerized during vacuum distillation. When heated with maleic anhydride, the substance gave a mixture of polymeric adducts (and was partly polymerized itself). Oxidation of the diene (I) with potassium permanganate gave the ketone (II) and oxalic acid.

The intermediate carbinol (III) has not been described in the literature either.

B.p. 70-72° at 9 mm, d_4^{20} 0.9348, n^{20}_D 1.4763, MR_D 45.94; calc. 46.46.

Calculated %: C 78.91; H 10.35; OH 11.19. $C_{10}H_{15}OH$. Calculated %: C 78.95; H 10.53.

For confirmation of the structure, the carbinol (III) was hydrogenated to the alcohol (IV) in the presence of $Pd/CaCO_3$ in ethanol at 20°. The alcohol (IV), which has not been described in the literature, was obtained by confirmatory synthesis from dicyclopropyl ketone (II) and propylmagnesium bromide. The infrared spectra of the two samples of (IV) were identical.

B.p. 78-80° at 9 mm, n^{20}_D 1.4646.

Found %: C 77.89; H 11.90; OH 12.69. $C_{10}H_{17}OH$. Calculated %: C 77.89; H 11.91; OH 11.02.

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BROMINATION AND ACYLATION OF PHENYLCYCLOPROPANE

R. Ya. Levina and P. A. Gembitskii

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
pp. 3480-3481, October, 1961
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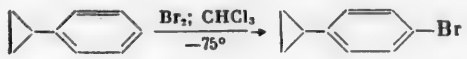
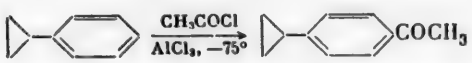
The nitration of phenylcyclopropane proceeds extremely vigorously even at −50° [1]. We studied another electrophilic replacement in the benzene ring, namely, bromination of phenylcyclopropane and showed that it proceeds smoothly under conditions where the reaction does not occur with benzene itself or alkylbenzenes.

The bromination of phenylcyclopropane was carried out with a dilute solution of bromine in chloroform at −75°, proceeded vigorously in the absence of a catalyst, and led to p-bromophenylcyclopropane (~80% yield, m.p. 15°, b.p. 116° at 15 mm, n^{20}_D 1.5752, d_4^{20} 1.3920, MR_D 46.82. $C_9H_9BrF_3\Delta$. Calculated 46.44).

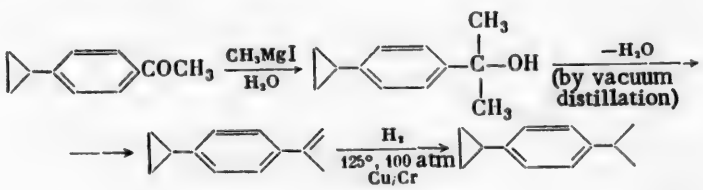


The structure of the bromide (its constants coincided with those of a sample of p-bromophenylcyclopropane obtained by another method [2]) was demonstrated by conversion to p-cyclopropylbenzoic acid (m.p. 160°, which corresponds to literature data [3]), p-cyclopropyltoluene (identical in constants and spectra with a preparation synthesized previously [4]), and p-cyclopropylethylbenzene (b.p. 92° at 10 mm, d_4^{20} 0.9215, n^{20}_D 1.5205, MR_D 48.26. $C_{11}H_{14}F_3\Delta$. Calculated 47.91).

We were also able to show that the acetylation of phenylcyclopropane by acetyl chloride in the presence of aluminum chloride proceeds extremely vigorously at the same temperature as bromination (at −75°) and gives a ~ 90% yield of p-acetylphenylcyclopropane* (m.p. 35° and b.p. 142° at 12 mm).



p-Acetylphenylcyclopropane was identified by conversion to p-cyclopropylcumene (the constants and spectra coincided with those of a sample synthesized previously [5]) and also by reduction by the Kizhner method to p-cyclopropylethylbenzene (the constants and Raman spectrum coincided with those of a preparation synthesized from p-bromophenylcyclopropane).



Thus, the benzene ring conjugated with the three-membered carbon ring in phenylcyclopropane has a superaromatic character in electrophilic substitution.

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* Hart and Levitt [2] carried out this reaction, beginning it at +4° and then cooling the mixture to −25° (ketone yield ~50%).

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SOME NEW DERIVATIVES OF CYCLIC β-DIKETONES

N. A. Domnin and N. S. Glebovskaya*

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
pp. 3481-3483, October, 1961
Original article submitted July 10, 1961

In previous communications [1] it was reported that cyclohexane-1,3-dione and 5,5-dimethylcyclohexane-1,3-dione (dimedone) do not give normal hydrazones with hydrazine hydrate and form only monohydrazones with unsym-dimethylhydrazine.

In the present work we studied the reaction of dimedone with phenylhydrazine, unsym-diphenylhydrazine, and semicarbazide.

It was established that dimedone and semicarbazide readily give normal dimedone bissemicarbazone with m.p. 212-213° (decomp.).

Found %: C 46.99, 47.25; H 7.49, 7.18; N 32.82, 32.94. $C_{10}H_{18}O_2N_6$. Calculated %: C 47.23; H 7.13; N 33.05.

The infrared spectrum contained a strong maximum at 3177 cm^{-1} (3.15 μ), corresponding to the valence vibrations of the NH group.

Dimedone gave only monohydrazones with phenylhydrazine and unsum-diphenylhydrazine.

Dimedone monophenylhydrazone: m.p. 165-167° (with decomp.).

Found • : C 67.94, 68.01; H 7.23, 7.10; N 11.62, 11.24. $C_{14}H_{18}ON_2$. Calculated • : C 68.27; H 7.37; N 11.37.

Infrared spectrum (in $CHCl_3$):

1525 cm^{-1} (6.55 μ); v.s.
1563 cm^{-1} (6.40 μ); s } Valence vibrations of >C=C< bonds of the aromatic nucleus

1590 cm^{-1} (6.30 μ); v.s. >C=O,

3181 cm^{-1} (3.14 μ); av. –NH–
3222 cm^{-1} (3.10 μ); w –OH.

Dimedone monodiphenylhydrazone: m.p. 220-220.5°.

Found %: C 78.11, 78.02; H 7.89; M 9.48, 9.60. $C_{20}H_{22}ON_2$. Calculated %: C 78.39; H 7.24; N 9.14.

Infrared spectrum (in $CHCl_3$):

1560 cm^{-1} (6.41 μ); v.s.
1590 cm^{-1} (6.30 μ); s } Valence vibrations of >C=C< bonds of the aromatic nucleus

1609 cm^{-1} (6.22 μ); v.s. >C=O,

3360 cm^{-1} (2.98 μ); av. –OH.

The infrared spectrum of dimedone monodimethylhydrazone [1] contains the following maxima:

1592 cm^{-1} (6.28 μ); v.s. >C=O,

3200 cm^{-1} (3.13 μ); av. –NH–,
3300 cm^{-1} (3.03 μ); av. –OH.

* Communication XXXVIII.

The maximum corresponding to the valence vibrations of the hydroxyl group was detected when the infrared spectrum of the monohydrazone in chloroform was plotted, but disappeared when the spectrum of a paste, i.e., a suspension in vaseline oil, was plotted. This is characteristic of all the dimedone monohydrazones and indicates the presence of keto-enol equilibrium in solution.

The infrared spectra of all the dimedone monohydrazones showed a strong displacement of the carbonyl group frequency into the long-wave region of the spectrum, which is characteristic of dimedone itself [2].

The reason why dimedone monophenylhydrazone and monodiphenylhydrazone do not react with a second molecule of the corresponding substituted hydrazine to give dihydrazones is evidently steric hindrance arising in this reaction.

The hypothesis was put forward that the anomalous behavior of cyclohexane-1,3-dione and dimedone in reactions with hydrazines is caused by the structure of the six-membered ring and the steric hindrance arising in it as a result of the presence of the substituents [1].

In this connection it seemed interesting to prepare a cyclic 1,3-diketone with substituents at the second carbon atom. It was established that the methylation of dimedone, in contrast to cyclohexane-1,3-dione [3], readily proceeds to full replacement of the hydrogens at the second carbon atom of the ring with the formation of 2,2,5,5-tetramethylcyclohexane-1,3-dione (dimethyldimedone) with m.p. 158-160°.

Found %: C 71.48, 71.30; H 9.55, 9.65. M 158.3, 163.2. $C_{10}H_{16}O_2$. Calculated %: C 71.40; H 9.59. M 168.2.

The infrared spectrum (in $CHCl_3$) contained a strong maximum at 1721 cm^{-1} (5.83 μ), corresponding to $\rangle C = O$, and the maximum characteristic of OH was completely absent.

In the methylation of dimedone, a very small amount of 2,5,5-trimethylcyclohexane-1,3-dione (methyldimedone) was obtained as a by-product:

B.p. 124 -125° (10 mm), n_D^{20} 1.0141, d_4^{20} 1.4897, MR_D 43.89; calc. 41.58 for keto-form and 42.63 for enol form.

Found %: C 70.18, 69.93; H 9.28, 9.02. M 154.0, 154.5. $C_9H_{14}O_2$. Calculated %: C 70.09; H 9.15. M 154.2.

Infrared spectrum:

1631 cm^{-1} (6.13 μ); s $\rangle C = O$ in enol form, conjugated with C = C;

1670 cm^{-1} (5.98 μ); v.s. $\rangle C = O$ in diketo form;

3291 cm^{-1} (3.04 μ); av. − OH in enol form.

Dimethyldimedone reacted readily with hydroxylamine to give dimethyldimedone dioxime with m.p. 226-229° (with decomp.).

Found %: C 60.33; H 9.35; N 14.74. $C_{10}H_{18}O_2N_2$. Calculated %: C 60.57; H 9.15; N 14.32.

It reacted with semicarbazide to form dimethyldimedone bissemicarbazone with m.p. 245-246° (with decomp.).

Found %: C 50.32, 50.48; H 7.99, 7.96. $C_{12}H_{22}O_2N_6$. Calculated %: C 51.04; H 7.86; N 29.77.

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COMMENTS ON THE ARTICLE OF BRESLOW AND CHIPMAN "SYNTHESIS OF CYCLOPROPENE DERIVATIVES BY D'YAKONOV'S METHOD"

I. A. D'yakonov and M. I. Komendantov

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
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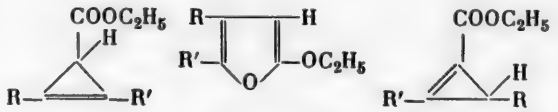
Original article submitted June 24, 1961

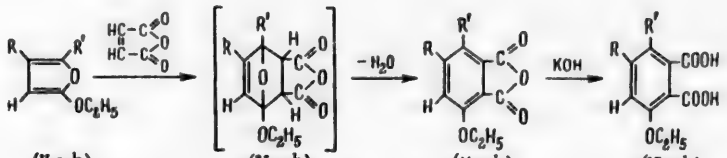
In the article of Breslow and Chipman [1] it was stated that in each pair of the isomeric compounds we obtained by the reaction of diazoacetic ester with acetylenic hydrocarbons [2], only one is a true derivative of cyclopropene (I), while the other is a substituted ethoxyfuran (II). In contradiction to this, in the preliminary communications we published, the formula of the isomeric cyclopropene (III) was proposed instead of the formula of the ethoxyfuran (II) [2-4].



(I, b—d*) (II, a—d) (III, a—d)

a) R=C$_6$H$_5$; R′=CH$_3$; b) R=R′=C$_6$H$_5$; c) R=R′=H=C$_3$H$_7$; d) R=R′=H . CuH$_2$.

In order to settle this dispute, we reinvestigated the compounds obtained and found that the point of view of Breslow and Chipman on their structure is correct. The investigation showed that the compounds to which the American chemists assigned the formulas of ethoxyfurans (II) readily undergo diene synthesis with maleic anhydride according to the following scheme:



(II, a, b) (IV, a, b) (V, a, b) (VI, a, b)

a) R=C$_6$H$_5$, R′=CH$_3$; b) R=R′=C$_6$H$_5$.

The adduct was found to be unstable and under the reaction conditions, it was converted into the anhydride (Va, b), alkaline hydrolysis of which yielded the acid (VIa, b).

(Va): yield 71.4% and m.p. 276-278°.

Found %: C 72.04, 72.16; H 5.02, 4.98; OC_2H_5 15.80, 15.68. $C_{15}H_9O_3(OC_2H_5)$. Calculated %: C 72.34; H 4.96; OC_2H_5 15.92.

(VIa): yield 75% and m.p. 124° (decomp.).

Found %: C 65.63; H 5.36; OC_2H_5 14.32. Equiv. 151.8. $C_{13}H_9OC_2H_5(COOH)_2$. Calculated %: C 65.81; H 5.19; OC_2H_5 14.52. Equiv. 150.1.

(Vb): yield 87.1% and m.p. 245-246°.

* Together with S. P. Korshunov, by now we have also studied the isomer (Ia).

Found %: C 76.49, 76.54; H 4.96, 4.74. $C_{20}H_{11}O_3OC_2H_5$. Calculated %: C 76.74; H 4.65.

(VIb): yield 95% and m.p. 65° (decomp.).

Found %: C 72.69; H 5.09. Equiv. 179.3. $C_{22}H_{18}O_5$. Calculated %: C 72.91; H 5.01. Equiv. 181.1.

The structure of the ethoxyfurans (IIa-d) was also confirmed by their resistance to the action of alkalis [2], the results of acid hydrolysis, oxidation with lead tetraacetate, and ozonization [2, 4]. In the infrared spectrum, the absorption bands at 1587 (v.s.) and 1621 (av) cm^{-1} indicated the presence of a diene structure [5].

The statement of the American chemists that we obtained the esters (Ib-d) by following the procedure developed by Breslow et al. is not correct. The latter authors used copper bronze as a catalyst for the synthesis of cyclopropene derivatives; we worked either without any catalyst or used very small amounts of copper sulfate for this purpose. In point of fact, we could not have copied the American authors as in their first brief communications [6, 7] Breslow et al. did not give any data either on the experimental conditions or on the conditions for the isolation of the final reaction products. We pointed this out in a brief communication published in Zhurnal Obshchei Khimii in May, 1959 (submitted to the Editor in January, 1959). The first information on the experimental conditions was given by Breslow et al. in March 1959 in the article "Darling's cyclopropene derivatives and their rearrangement" [8]. In addition, our experiments on the synthesis of cyclopropene derivatives differed from the experiments on Breslow et al. in that the American chemists never isolated the cyclopropenecarboxylic esters in the pure form, but converted the crude reaction product immediately into the corresponding acid; we always characterized the primary reaction products, i.e., the corresponding esters, and only then converted them into the acids.

In conclusion, we should note that the reaction products of diazoacetic ester and 1-phenylpropyne, which we described in the first communication [3], was a mixture of the two isomers (Ia) and (IIa) and not the pure isomer (Ia), as could be concluded [1] from preliminary data. The corrected constants for this product, which we gave in a subsequent communication [4], refer to the individual isomer (IIa).

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REPLY TO E. F. ZHURAVLEV

I. L. Krupatkin

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
pp. 3485-3486, October, 1961
Original article submitted May 18, 1961

In recent articles [1, 2] E. F. Zhuravlev has been developing a formal geometric approach to equilibria between liquid phases and has been extending it successively to various types of liquid-phase equilibrium. Meanwhile, R. V. Mertslin's principle of predominance, which has been accepted in science and generally recognized as the key to the understanding of multicomponent liquid systems, has been persistently supplanted by formal geometric concepts, which could be the subject of a separate article. In particular, in his recent discussion [3], E. F. Zhuravlev attempted to explain specific cases of layer formation by liquids, which we had examined earlier [4], from the above point of view using a geometric scheme for these systems.

In investigating particular cases of layer formation by liquids, in our article [4] we examined and partly explained a whole series of problems, namely, the cause of the formation and nature of compounds which melt with layer formation, the characteristics of their behavior in solutions, their stabilization and dissociation, their participation in the predominant systems and, finally, the formation of a two-phase liquid equilibrium in ternary systems including these compounds. To elucidate the latter problem, we first proposed two possible explanations on the basis of conjugate phase reactions, but, as is stated in the article, other explanations are possible due to the fact that the problem has not been investigated much. E. F. Zhuravlev substituted his "explanation" for the solution of this particular problem. His "explanation" does not elucidate the nature or properties of the compounds which melt with layer formation and form the basis of the phenomenon examined nor the participation of these compounds in the chemistry of the processes of the ternary system, and for this reason his explanation is quite unacceptable. Nonetheless, Zhuravlev puts forward his scheme as an all-embracing explanation and, without any grounds, completely rejects all the questions raised in our article while, essentially, offering no substitute.

Regarding the formal scheme itself, which Zhuravlev puts forward, it does not correspond to the elementary concepts on systems with layer formation or to their diagrams. Firstly, Zhuravlev states that binary systems with chemical compounds which melt with layer formation cannot exist independently in nature while the form of their diagrams can be only a cross section, i.e., part of a ternary system. But, in contradiction to Zhuravlev, such systems actually exist and about 20 such binary systems are now known. Secondly, Zhuravlev's arguments, which are divorced from natural systems, have led him to assert that the liquid phases coexisting in binary systems with layer formation are at different temperatures, i.e., that the tie lines are not parallel, but lie at a certain angle to the concentration axis, which never does and cannot occur in nature. Thirdly, seven metal binary systems with compounds which melt with layer formation are already known; the application of Zhuravlev's scheme to metal systems is absurd as it specifies that when two metals react, a new metal should form between them and not a compound. Thus, Zhuravlev's scheme is of a farfetched, formal geometric character; it is incompatible with experimental facts and is artificially imposed on natural phenomena and cannot be applied to actual ternary systems.

We should also add that the continuation of the equilibrium curves of a given ternary system into another adjacent ternary system has been claimed by Zhuravlev as his own, new idea. However, this fact has been generally known from the time when heterogeneous equilibria were first studied.

In conclusion, we should note that Zhuravlev states that we have developed a "theory" of particular cases of layer formation by liquids. This does not correspond at all to the facts: the development of such a theory requires the accumulation of experimental facts in this almost unknown field, and this is what we are now doing, but as long as no theory exists, as Zhuravlev states, there can be no argument against our theory.

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OBITUARY OF ACADEMICIAN R. LUKES

K. Bláha and M. Ferles

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 10,
pp. 3487-3489, October, 1961

Academician Rudolf Lukes, Doctor of Technical Sciences, Professor of Organic Chemistry in the Chemico-technological Institute in Prague, President of the Czechoslovakian Chemical Society, Laureate of the Czechoslovakian State Prize, member of a number of foreign chemical societies, and an outstanding organic chemist of the Czechoslovakian Socialist Republic, died on October 17, 1960, after a short illness.

Rudolf Lukes (born April 13, 1897 in Kralupy on the Vltava) started studying chemical literature while still in a secondary school. In 1914 he signed up to join the department of technical chemistry of the Czech Technical College in Prague but completed his studies only after the war as he was called up by the army. After defending his dissertation in an examination for the degree of Doctor of Technical Sciences (1923), he became an assistant in the Institute of General Experimental Chemistry of the Czech Technical College in Prague and later a lecturer in the department of organic chemistry in the Technical College and the university, while in 1939 he became head of the Institute of General Experimental Organic Chemistry of the Czech Technical College. After the forced closing of Czech higher institues by the German invaders (1939), Lukes worked in the factory laboratories of the Society of Chemical and Metallurgical Industry in Prague where he was head of the organic chemistry laboratory and read lectures to the students. After the war he became professor and was one of the first to be elected a member of the recently organized Czechoslovakian Academy of Sciences (in 1952), where he headed the heterocyclic compounds laboratory.

Lukes started his scientific activities under the direction of Professor Votochek in the field of sugar chemistry. His dissertation was part of a large series of papers on the optical activity of sugar derivatives, the final result of which was the well-known hydrazone rule of Votochek. However, Lukes was unsatisfied with this field where at that time the work consisted of the accumulation of empirical data. He therefore concentrated on a study of Robinson's theory on the biological genesis of alkaloids and started to work on its experimental justification.

He first developed convenient methods for synthesizing the starting materials. However, one of the reactions, namely, the Grignard reaction with N-methylsuccinimide attracted Lukes's attention and caused him to postpone the study of alkaloid biosynthesis to a later date. The Grignard reaction with N-methylsuccinimide, N-methylglutarimide, various pyrrolidones, pyrrolones, and piperidones opened a way to pyrrole and pyridine derivatives and was the basis for the synthesis of some alkaloids, but most important, provided a new method for the synthesis of aliphatic acids. The large selection of Grignard reagents offered extensive possibilities for the synthesis of higher homologs of aliphatic acids substituted with heterocyclic radicals and, finally, of dicarboxylic acids.

A thorough study of the differences in reactivity of carbonyl groups in cyclic imides (in which only one group reacts normally with the Grignard reagent while the other remains inert) made it possible to extend Bredt's prohibition to lactams. Bicyclic lactams in which the double bond in a mesomeric form of the amide group would be at the point of branching of the rings are formed only under certain conditions. The carbonyl group in them has a ketonic and not an amide character, despite the fact that it is directly adjacent to a nitrogen atom.

During the Second World War Lukes and his co-workers worked on another extensive group of problems connected with the chemical industry. At that time he initiated a study of the chemistry of furan which led to a number of practical results: he worked out a synthesis of pimelic acid by the electrochemical reduction of hydrochelidonic acid, prepared from furylacrylic acid. A synthesis of 2,5-furandicarboxylic acid, which was used for the production of artificial fibers of the terylene type, was developed.

Lukes devoted much work to the investigation of coal tar bases. Industrial methods for isolating some pyridine homologs were developed. This formed the basis for an investigation of the reduction of quaternary pyridinium salts by treatment with formic acid, and this made possible a cheap method of synthesizing piperideines and some pyrrole derivatives were then obtained from the latter.

Exhaustive methylation was used extensively in determining the position of the double bond in unsaturated cyclic bases. In this connection, the effect of steric factors on this type of cleavage was investigated (both for monocyclic and bicyclic compounds).

The establishment of a laboratory of heterocyclic compounds made it possible for Academician Lukes to investigate the biogenesis of alkaloids in which he had been interested before. A systematic analysis of the contemporary state of the problem led him to consider the study of the biogenesis of alkaloids on the basis of their stereochemical relations. First a general method was developed for determining the relative configuration of amino alcohols. In later work he established the relative configurations of a series of alkaloids and studied some reactions which could be considered as typical. Unfortunately, this work has remained unfinished.

The scientific activity of Lukes is inseparable from his teaching activities. He spared no pains to pass on to starting chemists some of his knowledge. He had many Czech and foreign students. Many of his students have achieved success in their chosen fields.

To all those who knew him, the late Professor Lukes will remain an example of a person who loved his work, nature, and people and who always strove for truth.

ERRATA

Vol. 31, Nos. 7-8, 1961

Page	Line	Reads	Should Read
1948	5 from bottom	$(RO)_3P\begin{matrix}Cl_3\\Cl\end{matrix}$	$(RO)_3P\begin{matrix}CCl_3\\Cl\end{matrix}$
1978 1978 1979	Table 1 Table 2 Tables 3 and 4	Nitrotolyl is given in all compounds	Nitrophenyl is given in all compounds
2085	Table, column 2, compound 17	$C_{22}H_{22}O_2NI$	$C_{22}H_{20}O_2NI$
2098	7 from bottom	$CH_3CH(OH)CH_2Cl2Na_2S_2O_3$	$CH_3CHOHCH_2Cl+2Na_2S_2O_3$
2182	18 from top	Triethylaluminum	Triphenyaluminum
2224	Table 1, column 7, 1 from top	$C_{31}H_{22}O_5N_2ClSP$	$C_{31}H_{22}O_5Cl_3SP$
2226	Table 2, column 7, 1 from top	$C_{31}H_{25}O_5N_2SP$	$C_{25}H_{21}O_5N_2SP$
2230	Table, column 1, 1 from bottom	$p\text{-}CH_3C_6H_4$	$p\text{-}CH_3OC_6H_4$
2231	Table, column 8, 3 from top	$C_{15}H_{25}O_2N_3P$	$C_{15}H_{26}O_2N_3P$
2231	Table, column 8, bottom line	$C_{17}H_{28}O_3N_3P$	$C_{16}H_{28}O_3N_3P$
2229	16 from bottom	$C_6H_5CONP(NC_6H_5)_3$	$C_6H_5CONP(NHC_6H_5)_3$
2329	Table 3, formular (XIV)	$p\text{-}C_4H_9SOCH_2CH_2SC_4H_3$	$p\text{-}C_4H_9SOCH_2CH_2SC_4H_9$
2341	Table 1, column 5, 1 from top	$C_2H_{18}O_3NSP$	$C_2H_{10}O_3NSP$
2353	Table, column 8, 2 from bottom	$C_{12}H_{21}O_6N^2SP$	$C_{12}H_{21}O_6N_2SP$
2373	17 from bottom	$C_{13}H_{17}O_2$	$C_3H_{17}O_2Cl$
2478	7 from top	$C_9H_{18}O_4P$	$C_9H_{18}O_4PCl$
2478	16 from top	$C_6H_9O_4PCl_2$	$C_7H_{13}O_4PCl_2$
2478	21 from top	$C_{17}H_{13}O_4PCl$	$C_7H_{13}O_4PCl_4$
2505	Table 1, column 1, 2 from bottom	$(C_2H)_2CH$	$(C_2H_5)_2CH$
2509	Caption to Figure 7	$CH_3CHRCOOC_2H_5$	$CH_3COCHRCOOC_2H_5$
2515	Table 2, column 2, compound 6	$HCOOO_2H_5$	$HCOOC_2H_5$
2578	17 from bottom	$C_{20}H_{19}N_2$	$C_{20}H_{19}O_2N$

SIGNIFICANCE OF ABBREVIATIONS MOST FREQUENTLY ENCOUNTERED IN SOVIET PERIODICALS

FIAN	Phys. Inst. Acad. Sci. USSR
GDI	Water Power Inst.
GITI	State Sci.-Tech. Press
GITTL	State Tech. and Theor. Lit. Press
GONTI	State United Sci.-Tech. Press
Gosenergoizdat	State Power Press
Goskhimizdat	State Chem. Press
GOST	All-Union State Standard
GTTI	State Tech. and Theor. Lit. Press
IL	Foreign Lit. Press
ISN (Izd. Sov. Nauk)	Soviet Science Press
Izd. AN SSSR	Acad. Sci. USSR Press
Izd. MGU	Moscow State Univ. Press
LEIIZhT	Leningrad Power Inst. of Railroad Engineering
LET	Leningrad Elec. Engr. School
LETI	Leningrad Electrotechnical Inst.
LETIIZhT	Leningrad Electrical Engineering Research Inst. of Railroad Engr.
Mashgiz	State Sci.-Tech. Press for Machine Construction Lit.
MEP	Ministry of Electrical Industry
MES	Ministry of Electrical Power Plants
MESEP	Ministry of Electrical Power Plants and the Electrical Industry
MGU	Moscow State Univ.
MKhTI	Moscow Inst. Chem. Tech.
MOPI	Moscow Regional Pedagogical Inst.
MSP	Ministry of Industrial Construction
NII ZVUKSZAPIOI	Scientific Research Inst. of Sound Recording
NIKFI	Sci. Inst. of Modern Motion Picture Photography
ONTI	United Sci.- Tech. Press
OTI	Division of Technical Information
OTN	Div. Tech. Sci.
Stroiizdat	Construction Press
TOE	Association of Power Engineers
TsKTI	Central Research Inst. for Boilers and Turbines
TsNIEL	Central Scientific Research Elec. Engr. Lab.
TsNIEL-MES	Central Scientific Research Elec. Engr. Lab.-Ministry of Electric Power Plants
TsVTI	Central Office of Economic Information
UF	Ural Branch
VIESKh	All-Union Inst. of Rural Elec. Power Stations
VNIIM	All-Union Scientific Research Inst. of Metrology
VNIIZhDT	All-Union Scientific Research Inst. of Railroad Engineering
VTI	All-Union Thermotech. Inst.
VZEI	All-Union Power Correspondence Inst.

NOTE: Abbreviations not on this list and not explained in the translation have been transliterated, no further information about their significance being available to us. –Publisher.

Soviet Journals Available in Cover-to-Cover Translation

ABBREVIATION	RUSSIAN TITLE	TITLE OF TRANSLATION	PUBLISHER	TRANSLATION BEGAN Vol.	Issue	Year
AÉ	Atomnaya énergiya	Soviet Journal of Atomic Energy	Consultants Bureau	1	1	1956
Akust. zh.	Akusticheskii zhurnal	Soviet Physics – Acoustics	American Institute of Physics	1	1	1955
	Antibiotiki	Antibiotics	Consultants Bureau	4	1	1959
Astr(on). zh(urn).	Astronomicheskii zhurnal	Soviet Astronomy–AJ	American Institute of Physics	34	1	1957
Avto(mat). svarka	Avtomaticheskaya svarka	Automatic Welding	British Welding Research Association (London)		1	1959
	Avtomatika i Telemekhanika	Automation and Remote Control	Instrument Society of America	27	1	1956
	Biofizika	Biophysics	National Institutes of Health*		1	1957
	Biokhimiya	Biochemistry	Consultants Bureau	21	1	1956
Byull. éksp(erim). biol. i med.	Byulleten' éksperimental'noi biologii i meditsiny	Bulletin of Experimental Biology and Medicine	Consultants Bureau	41	1	1959
DAN (SSSR) } Dokl(ady) AN SSSR }	Doklady Akademii Nauk SSSR	The translation of this journal is published in sections, as follows:				
		Life Sciences: Doklady Biochemistry Section	American Institute of Biological Sciences	106	1	1956
		Life Sciences: Doklady Biological Sciences Sections (Includes: Anatomy, biophysics, cytology, ecology, embryology, endocrinology, evolutionary morphology, genetics, histology, hydrobiology microbiology, morphology, parasitology, physiology, zoology sections)	American Institute of Biological Sciences	112	1	1957
		Life Sciences: Doklady Botanical Sciences Sections (Includes: Botany, phytopathology, plant anatomy, plant ecology, plant embryology, plant physiology, plant morphology sections)	American Institute of Biological Sciences	112	1	1957
		Chemical Sciences: Proceedings of the Academy of Sciences of the USSR, Section: Chemical Technology	Consultants Bureau	106	1	1956
		Chemical Sciences: Proceedings of the Academy of Sciences of the USSR, Section: Chemistry	Consultants Bureau	106	1	1956
		Chemical Sciences: Proceedings of the Academy of Sciences of the USSR, Section: Physical Chemistry	Consultants Bureau	112	1	1957
		Earth Sciences: Doklady Earth Sciences Sections (Includes: Geochemistry, geology, geophysics, hydrogeology, mineralogy, paleontology, petrography, permafrost sections)	American Geological Institute	124	1	1959
		Earth Sciences: Proceedings of the Academy of Sciences of the USSR, Section: Geochemistry	Consultants Bureau	106-123	1-6	1957-1958
		Earth Sciences: Proceedings of the Academy of Sciences of the USSR, Sections: Geology	Consultants Bureau	106-123	1-6	1957-1958
		Mathematics: Doklady Soviet Mathematics	The American Mathematics Society	131	1	1961
		Physics: Soviet Physics–Doklady (Includes: Aerodynamics, astronomy, crystallography, cybernetics and control theory, electrical engineering, energetics, fluid mechanics, heat engineering, hydraulics, mathematical physics, mechanics, physics, technical physics, theory of elasticity sections)	American Institute of Physics	106	1	1956
		Physics: Proceedings of the Academy of Sciences of the USSR, Applied Physics Sections (does not include mathematical physics or physics sections)	Consultants Bureau	106-117	1	1956-1957
Derevoobrabat. prom-st'.	Derevoobrabatyvayushchaya promyshlennost'	Wood Processing Industry	Timber Development Association (London)		9	1959
	Élecktrosvyaz	Telecommunications	Massachusetts Institute of Technology*		1	1957
Éntom(ol). oboz(renie)	Éntomologicheskoe obozrenie	Entomological Review	American Institute of Biological Sciences	38	1	1959
Farmakol. (i) toksikol(ogiya)	Farmakologiya i toksikologiya	Pharmacology and Toxicology	Consultants Bureau	20	1	1957
FMM	Fizika metallov i metallovedenie	Physics of Metals and Metallography	Acta Metallurgica*	5	1	1957
Fiziol. zhurn. SSSR (im. Sechenova)	Fiziologicheskii zhurnal im. I. M. Sechenova	Sechenov Physiological Journal USSR	National Institutes of Health*		1	1957
Fiziol(ogiya) rast.	Fiziologiya rastenii	Plant Physiology	American Institute of Biological Sciences	4	1	1957
	Geokhimiya	Geochemistry	The Geochemical Society		1	1958
FTT	Fizika tverdogo tela	Soviet Physics–Solid State	American Institute of Physics	1	1	1959
Izmerit. tekh(nika)	Izmeritel'naya tekhnika	Measurement Techniques	Instrument Society of America		1	1959
Izv. AN SSSR, O(td). Kh(im). N(auk)	Izvestiya Akademii Nauk SSSR: Otdelenie khimicheskikh nauk	Bulletin of the Academy of Sciences of the USSR: Division of Chemical Sciences	Consultants Bureau		1	1952

continued

Izv. AN SSSR, O(td). T(ekhn). N(auk): Met(all). i top.	(see Met. i top.)				
Izv. AN SSSR Ser. fiz(ich).	Izvestiya Akademii Nauk SSSR: Seriya fizicheskaya	Bulletin of the Academy of Sciences of the USSR: Physical Series	Columbia Technical Translations	1	1954
Izv. AN SSSR Ser. geofiz.	Izvestiya Akademii Nauk SSSR: Seriya geofizicheskaya	Bulletin (Izvestiya) of the Academy of Sciences USSR: Geophysics Series	American Geophysical Union	1	1954
Izv. AN SSSR Ser. geol.	Izvestiya Akademii Nauk SSSR: Seriya geologicheskaya	Izvestiya of the Academy of Sciences of the USSR: Geologic Series	American Geological Institute	1	1958
Kauch. i rez.	Kauchuk i rezina	Soviet Rubber Technology	Research Association of British Rubber Manufacturers	18	1 1959
	Kinetika i kataliz	Kinetics and Catalysis	Consultants Bureau	1	3 1960
	Koks i khimiya	Coke and Chemistry USSR	Coal Tar Research Association (Leeds, England)		1 1958
Kolloidn. zh(urn).	Kolloidnyi zhurnal	Colloid Journal	Consultants Bureau	14	1 1952
	Kristallografiya	Soviet Physics – Crystallography	American Institute of Physics	2	1 1957
Metalov. i term. obrabot. metal.	Metallovedenie i termicheskaya obrabotka metallov	Metal Science and Heat Treatment of Metals	Acta Metallurgica	6	1 1958
	Metallurg	Metallurgist	Acta Metallurgica		1 1957
Met. i top.	Metallurgiya i topliva	Russian Metallurgy and Fuels	Eagle Technical Publications		1 1960
Mikrobiol.	Mikrobiologiya	Microbiology	American Institute of Biological Sciences	26	1 1957
OS	Optika i spektroskopiya	Optics and Spectroscopy	American Institute of Physics		6 1959
	Pochvovedenie	Soviet Soil Science	American Institute of Biological Sciences		1 1958
	Priborostroenie	Instrument Construction	British Scientific Instrument Research Association		1 1959
Pribory i tekhn. éks(perimenta)	Pribory i tekhnika éksperimenta	Instruments and Experimental Techniques	Instrument Society of America		1 1957
Prikl. matem. i mekh.	Prikladnaya matematika i mekhanika	Applied Mathematics and Mechanics	American Society of Mechanical Engineers		1 1958
PTÉ	(see Pribory i tekhn. éks.)				
	Problemy Severa	Problems of the North	National Research Council of Canada		
Radiotekh.	Radiotekhnika	Radio Engineering	Massachusetts Institute of Technology*	12	1 1957
Radiotekh. i élektronika	Radiotekhnika i élektronika	Radio Engineering and Electronics	Massachusetts Institute of Technology*	2	1 1957
	Stanki i instrument	Machines and Tooling	Production Engineering Research Assoc.		1 1959
	Stal'	Stal (In English)	Iron and Steel Institute		1 1959
Stek. i keram.	Steklo i keramika	Glass and Ceramics	Consultants Bureau	13	1 1956
Svaroch. proiz-vo	Svarochnoe proizvodstvo	Welding Production	British Welding Research Association		4 1959
Teor. veroyat. i prim.	Teoriya veroyatnostei i ee primenenie	Theory of Probability and Its Applications	Society for Industrial and Applied Mathematics		1 1956
Tsvet. Metally	Tsvetnye metally	Nonferrous Metals	Primary Sources		1 1960
UFN	Uspekhi fizicheskikh Nauk	Soviet Physics – Uspekhi (partial translation)	American Institute of Physics	66	1 1958
UKh	Uspekhi khimii	Russian Chemical Reviews	The Chemical Society (London)		1 1960
UMN	Uspekhi matematicheskikh nauk	Russian Mathematical Surveys	London Mathematical Society	15	1 1960
Usp. fiz. nauk	(see UFN)				
Usp. khim(ii)	(see UKh)				
Usp. matem. nauk	(see UMN)				
Usp. sovr. biol.	Uspekhi sovremennoi biologii	Russian Review of Biology	Oliver and Boyd	48	1959
Vest. mashinostroeniya	Vestnik mashinostroeniya	Russian Engineering Journal	Production Engineering Research Assoc.	4	1959
Vop. gem. i per. krovi	Voprosy gematologii i perelivaniya krovi	Problems of Hematology and Blood Transfusion	National Institutes of Health*		1 1957
Vop. onk.	Voprosy onkologii	Problems of Oncology	National Institutes of Health*		1 1957
Vop. virusol.	Voprosy virusologii	Problems of Virology	National Institutes of Health*		1 1957
Zav(odsk). lab(oratoriya)	Zavodskaya laboratoriya	Industrial Laboratory	Instrument Society of America	25	1 1959
ZhAKh Zh. anal(it). khimii	Zhurnal analiticheskoi khimii	Journal of Analytical Chemistry USSR	Consultants Bureau	7	1 1952
ZhETF Zh. éksperim. i teor. fiz.	Zhurnal éksperimental'noi i teoreticheskoi fiziki	Soviet Physics–JETP	American Institute of Physics	28	1 1955
ZhFKh Zh. fiz. khimii	Zhurnal fizicheskoi khimii	Russian Journal of Physical Chemistry	The Chemical Society (London)		7 1959
ZhMÉI Zh(urn). mikrobiol. épidemiol. i immunobiol.	Zhurnal mikrobiologii, épidemiologii i immunobiologii	Journal of Microbiology, Epidemiology and Immunobiology	National Institutes of Health*		1 1957
ZhNKh Zh(urn). neorgan(ich). khim(ii)	Zhurnal neorganicheskoi khimii	The Russian Journal of Inorganic Chemistry	The Chemical Society (London)		1 1959
ZhOKh Zh(urn). obshch(ei) khimii	Zhurnal obshchei khimii	Journal of General Chemistry USSR	Consultants Bureau	19	1 1949
ZhPKh Zh(urn). prikl. khimii	Zhurnal prikladnoi khimli	Journal of Applied Chemistry USSR	Consultants Bureau	23	1 1950
ZhSKh Zh(urn). strukt. khimii	Zhurnal strukturnoi khimii	Journal of Structural Chemistry	Consultants Bureau	1	1 1960
ZhTF Zh(urn). tekhn. fiz.	Zhurnal teknicheskoi fiziki	Soviet Physics–Technical Physics	American Institute of Physics	26	1 1956
Zh(urn). vyssh. nervn. deyat. (im. Pavlova)	Zhurnal vysshei nervnoi deyatel'nosti (im. I. P. Pavlova)	Pavlov Journal of Higher Nervous Activity	National Institutes of Health*		1 1958

*Sponsoring organization. Translation through 1960 issues is a publication of Pergamon Press.

INFRARED SPECTRA OF CELLULOSE AND ITS DERIVATIVES

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Translated from Russian by A. B. Densham

Corrected and updated by the author for the American edition.

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